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Trace 24801

Supplementary Material

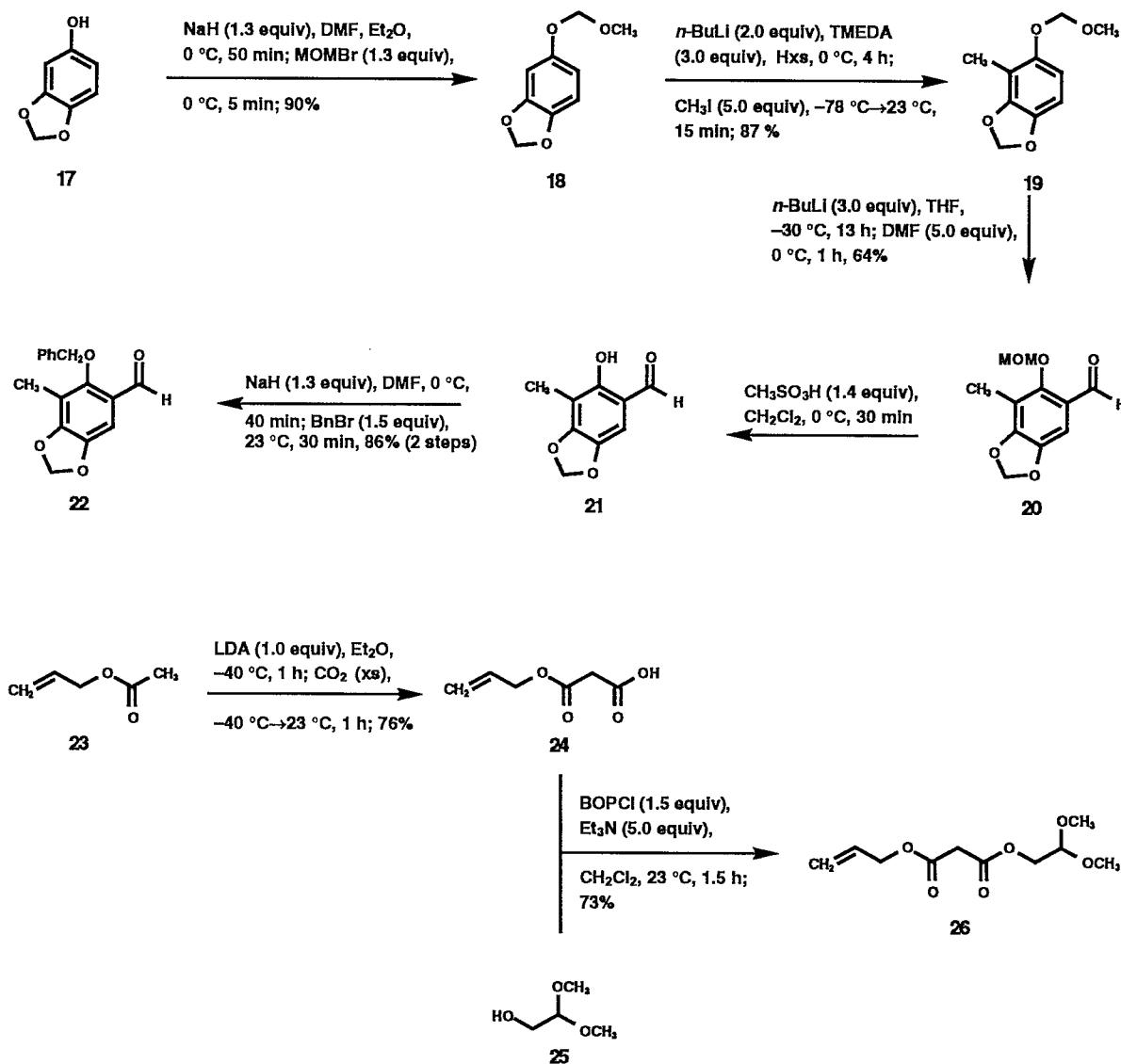
Supplementary Material

Enantioselective Total Synthesis of Ecteinascidin 743

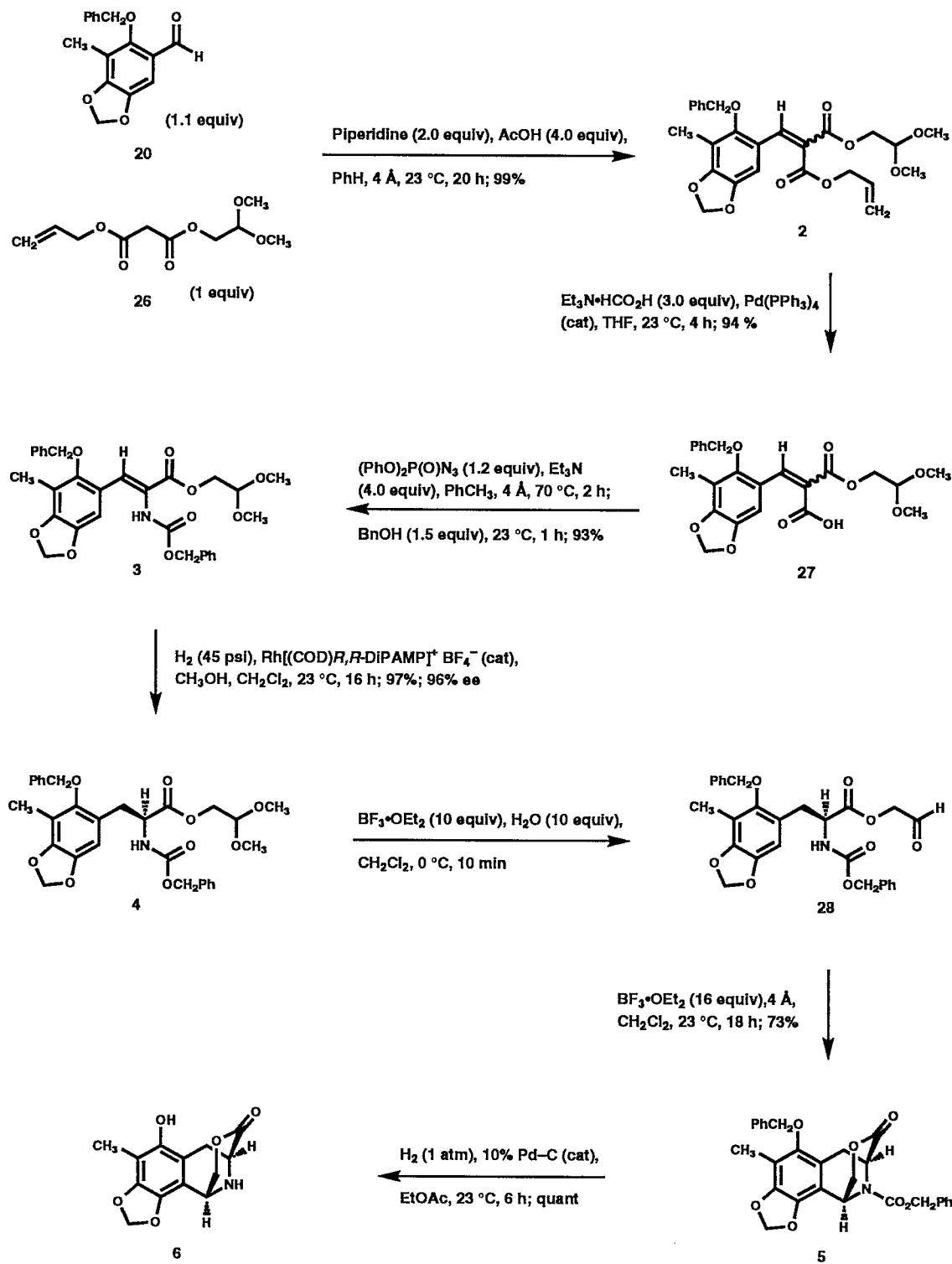
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Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

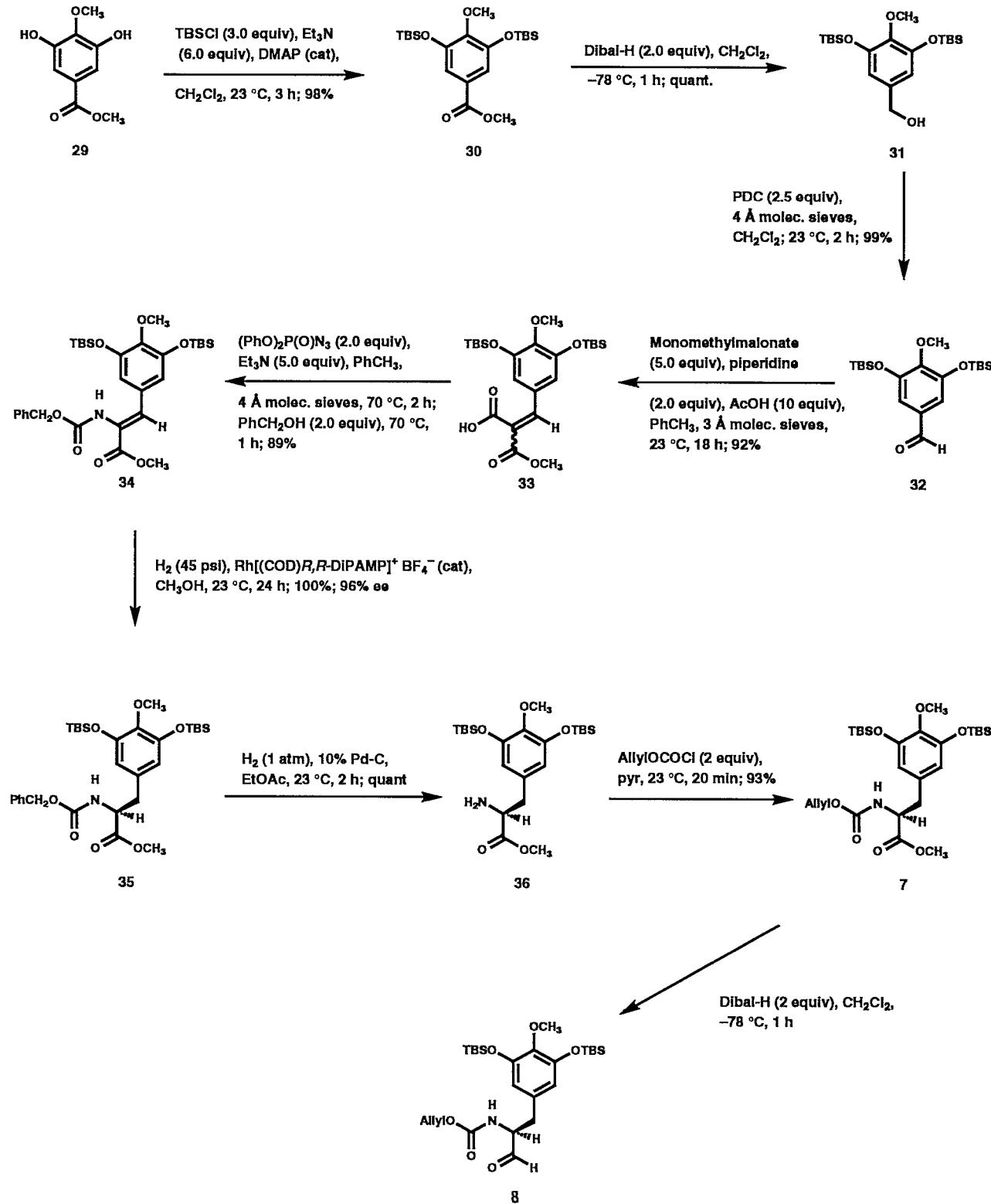
Left Fragment I



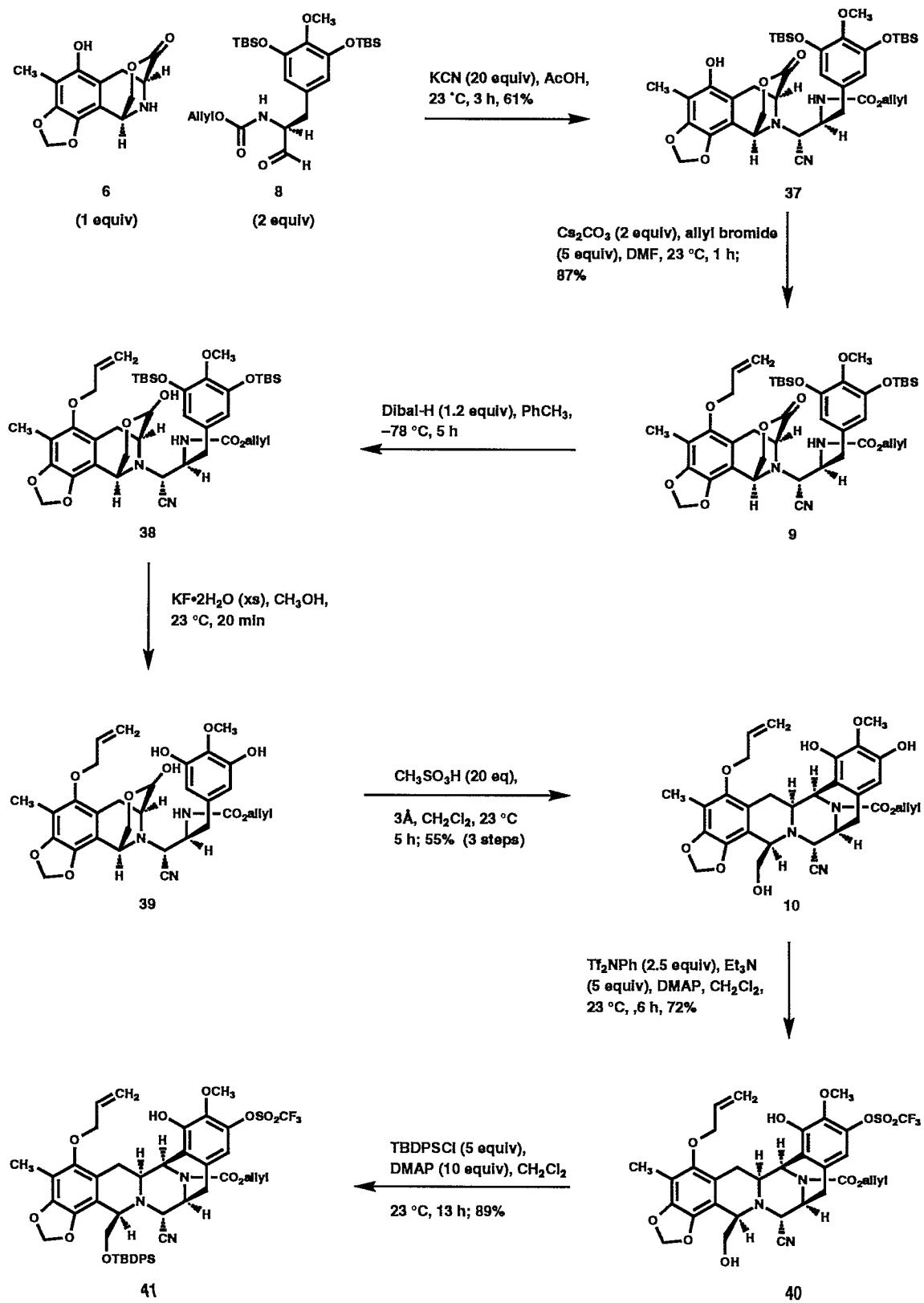
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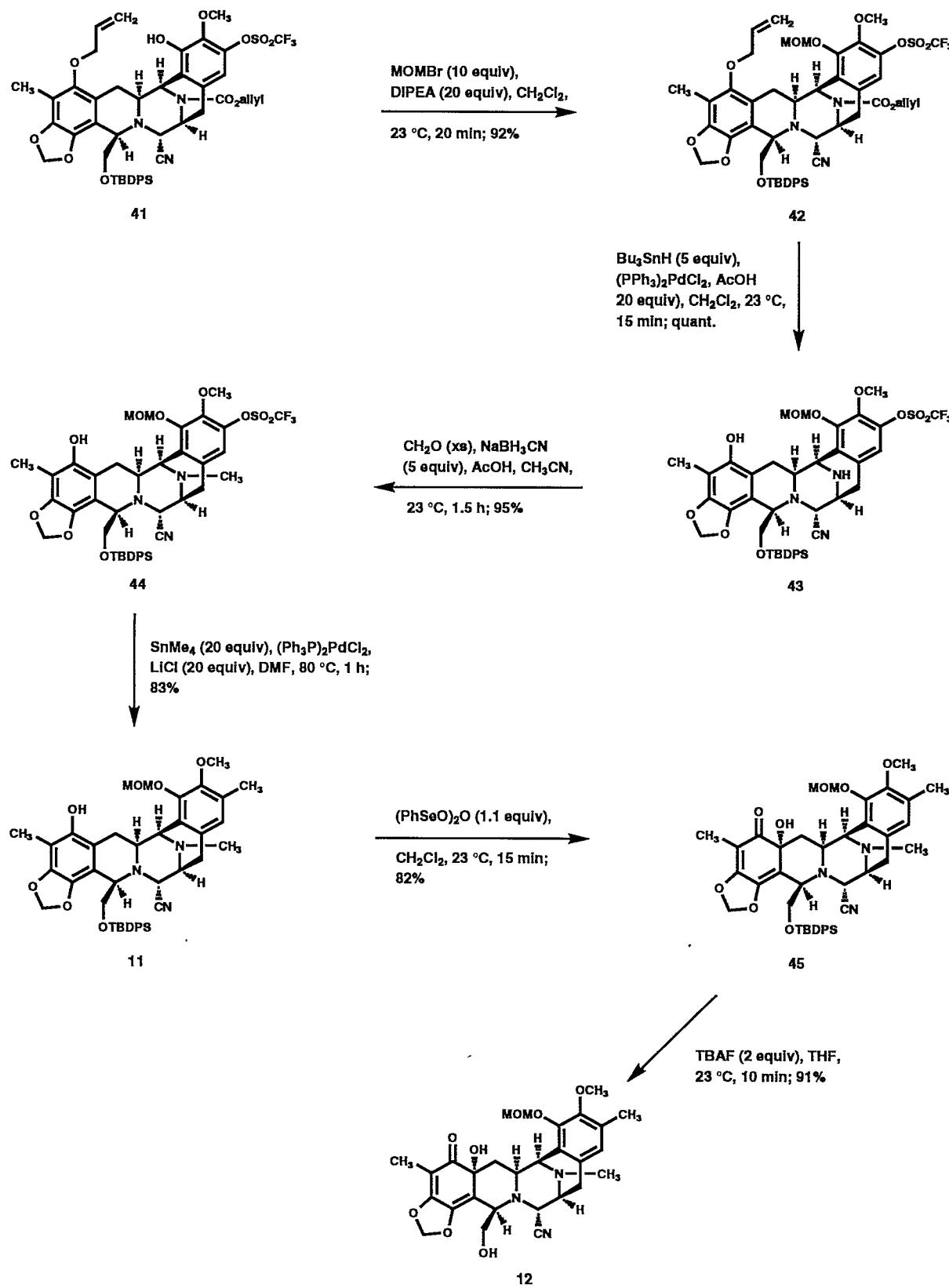
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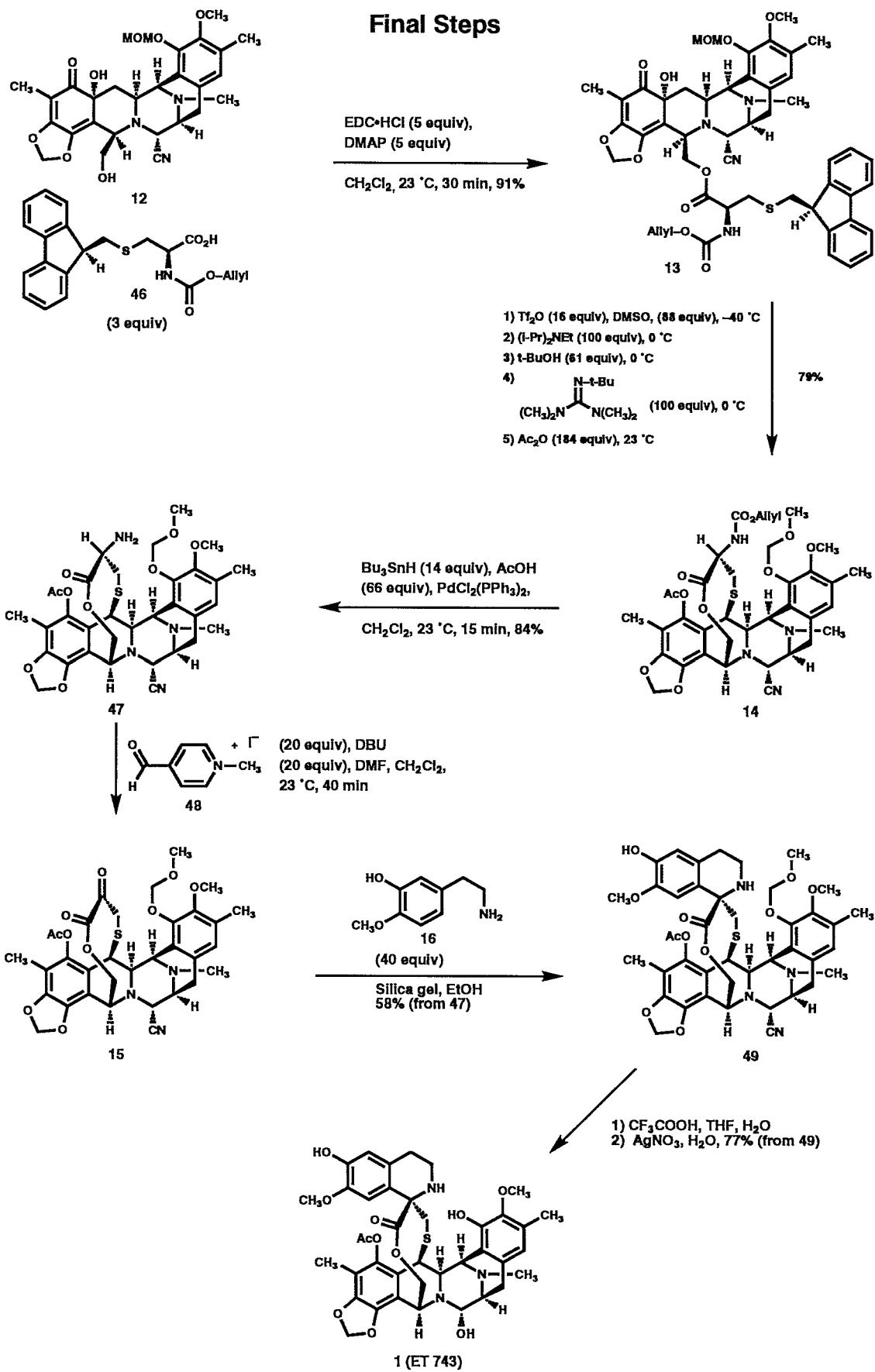


Pentacycle I



Pentacycle II





General Procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation/argon flush cycles (greater than three iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at *ca.* 25 Torr. Flash column chromatography was performed as described by Still *et al.* employing 230-400 mesh silica gel.¹ Thin-layer chromatography (analytical and preparative) was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, hexanes, *N,N*-diisopropylethylamine, diisopropylamine, triethylamine, pyridine, toluene, benzene, TMEDA, piperidine, and acetonitrile were distilled from calcium hydride at 760 Torr. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).²

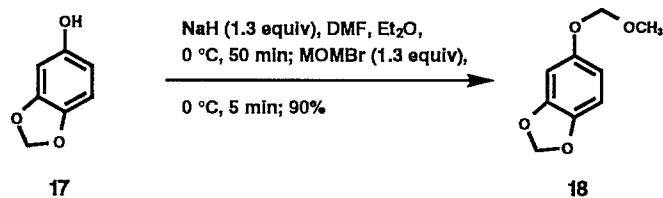
Instrumentation. Infrared (IR) spectra were obtained using a Nicolet 5ZDX FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm⁻¹), and intensity of absorption (s = strong, m = medium, w = weak). Proton and carbon-13 nuclear magnetic resonance (¹H NMR or ¹³C NMR) spectra were recorded with a Bruker AM500 (500 MHz), a Bruker AM400 (400 MHz), or a Bruker AM300 (300 MHz) NMR spectrometer; chemical shifts are expressed in parts per

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923.

² Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* 1976, 41, 1879.

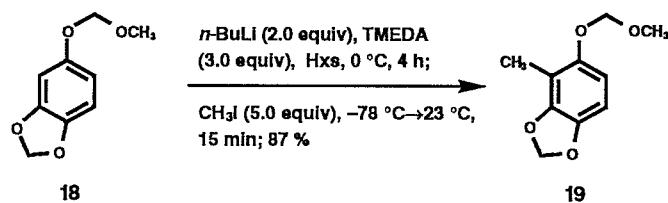
million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl_3 : δ 7.26, C_6HD_5 : δ 7.20, CDHCl_2 : δ 5.38, $\text{CD}_3\text{COCD}_2\text{H}$: δ 2.04, CD_2HOD : δ 3.30). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = quartet, m = multiplet and/or multiple resonances), integration, coupling constant in Hertz (Hz), and assignment. Chiral high performance liquid chromatography (HPLC) was conducted with an Isco 2350 equipped with the specified column (see experimentals). Melting points were recorded with a Fisher-Johns melting point apparatus and are uncorrected.

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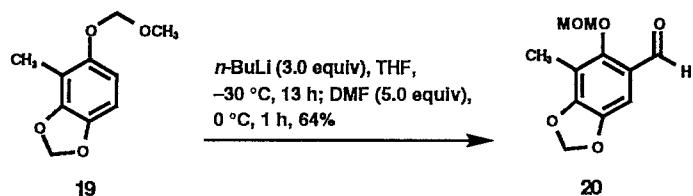


Methoxymethyl Ether 18. To a solution of **17** (10.2 g, 74.3 mmol, 1 equiv) in a mixture of ethyl ether and DMF (4:1 (v/v), 100 mL) at 0 °C was added a suspension of sodium hydride in mineral oil (57% (w/w), 4.07 g, 96.6 mmol, 1.3 equiv). The resulting suspension was stirred at 0 °C for 35 min, and then bromomethylmethyl ether (7.89 mL, 96.6 mmol, 1.3 equiv) was added dropwise. The suspension was stirred at 0 °C for 5 min and then at 23 °C for 1 h before the excess sodium hydride was neutralized with the slow addition of methyl alcohol (5 mL) at 0 °C. The solution was partitioned between ethyl acetate (500 mL) and water (300 mL), and the organic phase was then washed with saturated aqueous sodium chloride solution (200 mL), dried (sodium sulfate), and concentrated. The residue was purified by flash column chromatography (7% ethyl acetate in hexanes) to afford **18** (13.1 g, 90%) as a colorless oil. R_f 0.32 (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 6.70 (d, 1H, J = 8.4 Hz, ArH), 6.62 (d, 1H, J = 2.4 Hz, ArH), 6.49 (dd, 1H, J = 8.4, 2.4 Hz, ArH), 5.91 (s, 2H, ArOCH_2OAr), 5.10 (s, 2H, MOM CH_2), 3.50 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 152.5, 148.1,

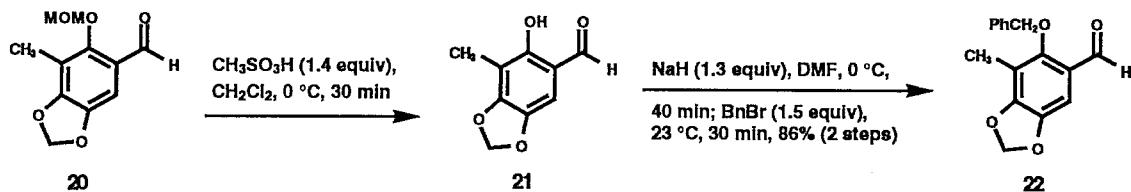
142.5, 108.5, 108.0, 101.1, 99.7, 95.5, 60.3, 55.8, 14.1; IR (neat film) 2990 (m), 2847 (m), 2827 (m), 1632 (m), 1611 (m), 1502 (s), 1486 (s), 1451 (m), 1245 (s), 1213 (s), 1152 (s), 1069 (s), 1004 (s), 922 (s) cm^{-1} ; HRMS (EI $^+$) m/z : calcd for $\text{C}_9\text{H}_{10}\text{O}_4$ (M^+) 182.0578, found 182.0582.



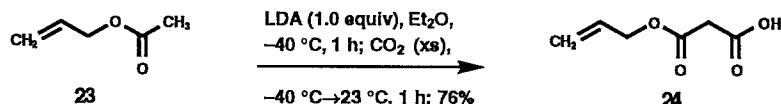
Methoxymethyl Ether 19. To a solution of **18** (6.76 g, 37.1 mmol, 1 equiv) and tetramethylethylenediamine (16.8 mL, 111 mmol, 3.0 equiv) in hexanes (70 mL) at 0 °C was added dropwise a solution of *n*-butyllithium (1.55 M in hexanes, 72.0 mL, 74.2 mmol, 2.0 equiv), and the resulting yellow suspension was stirred at 0 °C for 2.5 h. A solution of iodomethane (11.5 mL, 186 mmol, 5.0 equiv) in diethyl ether (12 mL) was added dropwise at 0 °C, and the resulting slurry was stirred at 23 °C for 1 h before it was quenched with the slow addition of water (10 mL). The reaction mixture was diluted with diethyl ether (500 mL), the product solution was washed sequentially with water (50 mL) and saturated aqueous sodium chloride solution (50 mL), and then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 2% \rightarrow 3% ethyl acetate in hexanes) to afford **19** (6.32 g, 87%) as a pale yellow oil. R_f 0.31 (10% ethyl acetate in hexanes); ^1H NMR (500 MHz, CDCl_3) δ 6.57 (d, 1H, J = 8.5 Hz, ArH), 6.51 (d, 1H, J = 8.5 Hz, ArH), 5.91 (s, 2 H, ArOCH_2OAr), 5.11 (s, 2H, MOM CH_2), 3.49 (s, 3H, OCH_3), 2.14 (s, 3H, ArCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 151.0, 146.6, 141.9, 110.7, 106.7, 104.8, 100.9, 95.7, 56.0, 8.9; IR (neat film) 2928 (w), 1479 (s), 1468 (s), 1242 (s), 1155 (m), 1103 (s), 1068 (s), 1020 (m), 988 (m), 793 (w) cm^{-1} ; HRMS (EI $^+$) m/z : calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$ (M^+) 196.0735, found 196.0729.



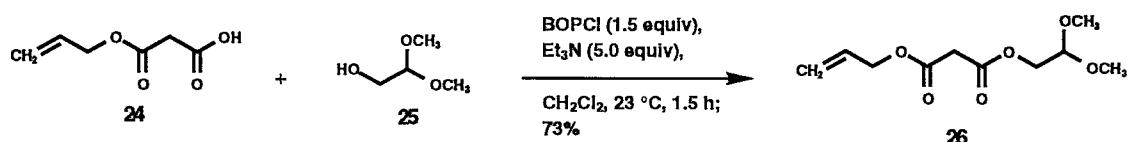
Aldehyde 20. To a solution of **19** (7.50 g 38.3 mmol, 1 equiv) in a 1:1 (v/v) mixture of diethyl ether and hexanes (70 mL) at 0 °C was added dropwise a solution of *n*-butyllithium (1.50 M in hexanes, 77.0 mL, 115 mmol, 3.0 equiv). The reaction mixture was allowed to warm to 23 °C and was stirred at this temperature for 5 h. The yellow suspension was cooled to –10 °C, and *N,N*-dimethylformamide (14.7 μL, 191 mmol, 5.0 equiv) then was added. The resulting solution was stirred at 23 °C for 1 h. Excess base was neutralized by the slow addition of glacial acetic acid (10 mL) at 0 °C, and the resulting suspension was stirred at 23 °C for 5 min. The reaction mixture was diluted with ethyl acetate (500 mL), and the product solution was washed sequentially with saturated aqueous sodium bicarbonate solution (400 mL), water (400 mL), and saturated sodium chloride solution (300 mL). The organic phase was dried (sodium sulfate) and concentrated, and the product **20** was crystallized from 10% ethyl acetate in hexanes (4.05 g). The mother liquor was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford additional **20** (1.35 g) (64% total) as a pale yellow solid (mp 91.5 °C). R_f 0.22 (ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 10.15 (s 1H, CHO), 7.13 (s, 1H, ArH), 6.03 (s, 2H, ArOCH_2OAr), 5.03 (s, 2H, MOM CH_2), 3.59 (s, 3H, OCH_3), 2.19 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 189.0, 157.0, 152.4, 144.2, 123.8, 113.7, 103.3, 102.1, 101.3, 58.0, 9.4; IR (neat film) 2925 (w), 1670 (s), 1614 (w), 1473 (m), 1452 (m), 1399 (m), 1280 (m), 1155 (m), 1059 (m), 935 (s), 927 (s), 860 (m) cm^{-1} ; HRMS (EI $^+$) m/z : calcd for $\text{C}_{11}\text{H}_{12}\text{O}_5$ (M^+) 224.0684, found 224.0684.



Aldehyde 22. To a solution of **20** (3.70 g, 16.5 mmol, 1 equiv) in dichloromethane (50 mL) and water (1.0 mL) at 0 °C was added methanesulfonic acid (1.50 mL, 22.5 mmol, 1.4 equiv). The reaction mixture was then neutralized with saturated aqueous sodium bicarbonate solution (50 mL) at 0 °C, and the resulting mixture was partitioned between saturated aqueous sodium bicarbonate solution (400 mL) and dichloromethane (3 x 200 mL). The combined organic layers were dried (sodium sulfate) and concentrated to afford **21** as a crude intermediate. To a solution of **21** in *N,N*-dimethylformamide (16.0 mL) at 0 °C was added a suspension of sodium hydride in mineral oil (57% (w/w), 903 mg, 21.5 mmol, 1.3 equiv), and the resulting suspension was stirred at 0 °C for 40 min. Benzyl bromide (2.94 mL, 24.8 mmol, 1.5 equiv) was added to the reaction mixture at 0 °C, and the resulting suspension was stirred at 23 °C for 30 min. Excess base was neutralized by the slow addition of methanol (2.0 mL) at 0 °C, and the reaction mixture was diluted with ethyl acetate (250 mL). The product solution was washed sequentially with water (200 mL) and saturated aqueous sodium chloride solution (200 mL), then was dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford **22** (3.85 g, 86%) as a viscous syrup. R_f 0.18 (10% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 10.08 (s, 1H, CHO), 7.40 (m, 5H, Bn ArH), 7.12 (s, 1H, ArH), 6.04 (s, 2H, ArOCH₂OAr), 4.93 (s, 2H, Bn CH₂), 1.60 (s, 3H, ArCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 188.5, 158.3, 152.6, 144.1, 135.7, 128.7, 128.3, 123.6, 113.8, 103.2, 102.1, 78.5, 11.8, 9.1; IR (neat film) 2923 (w), 1674 (s), 1612 (w), 1470 (m), 1420 (m), 1375 (m), 1352 (m), 1278 (s), 1170 (m), 1096 (s), 1069 (m) cm^{-1} ; HRMS (EI⁺) m/z : calcd for $\text{C}_{16}\text{H}_{14}\text{O}_4$ (M^+) 270.0892, found 270.0892.

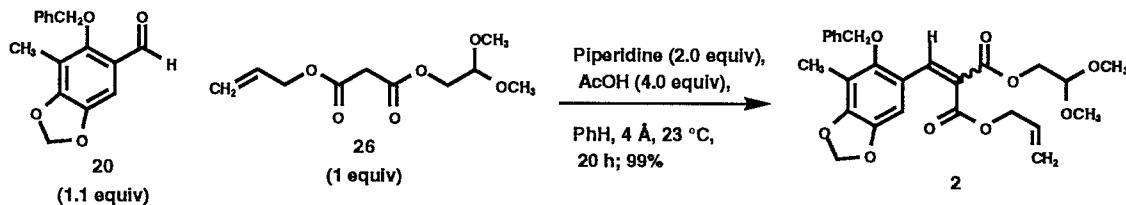


Monoallylmalonate 24. A solution of *n*-butyllithium (1.56 M in hexanes, 19.2 mL, 30.0 mmol, 1.0 equiv) was added to a solution of diisopropylamine (5.47 mL, 39.0 mmol, 1.3 equiv) in ethyl ether (30.0 mL) at -78 °C. The reaction flask was transferred briefly to an ice bath (10 min), and then was recooled to -78 °C. Allyl acetate **23** (3.23 mL, 30.0 mmol, 1 equiv) was added to the cold solution of lithium diisopropylamide, and the resulting solution was stirred at -40 °C for 1 h. The reaction mixture was cooled to -78 °C and excess solid carbon dioxide was added to the reaction mixture before it was allowed to warm to 23 °C over a 1 h period. The turbid solution was diluted with water (100 mL) and was washed with ethyl ether (3 x 50 mL). The aqueous layer was acidified at 0 °C to pH=2 with the slow addition of concentrated hydrochloric acid and then was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated to afford crude acid **24** (3.35 g, 76%) as a pale yellow oil, which was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 5.92 (m, 1H, CH₂=CH-), 5.36 (m, 1H, CH₂=CH-), 5.27 (m, 1H, CH₂=CH-), 4.68 (dt, 2H, *J* = 5.7, ~1 Hz, CH₂=CHCH₂-), 3.48 (s, 2H, CH₂); IR (neat film) 3300-2400 (m), 1744 (s), 1322 (m), 1156 (m) cm⁻¹.



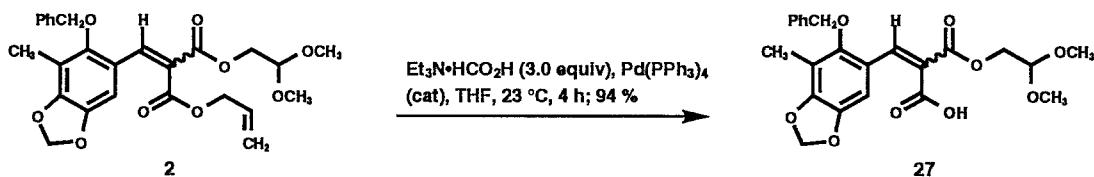
Allyl-2,2-dimethoxyethyl Malonate 26. To a solution of acid **24** (7.50 g, 52.0 mmol, 1 equiv), 2,2-dimethoxyethanol (**25**) (5.50 g, 52.0 mmol, 1.0 equiv), and triethylamine (36.0, 258 mmol, 5.0 equiv) in dichloromethane (100 mL) was added solid BOPCl (20.0 mg, 78.7 mmol, 1.5 equiv), and the resulting slurry was stirred at 23 °C for 1 h. The reaction mixture was filtered, the filtrate was diluted with ethyl acetate (400 mL), and the product solution was washed sequentially with water (2 x 300 mL) and saturated

aqueous sodium chloride solution (300 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 20–33% ethyl acetate in hexanes) to afford **26** (8.81 g, 73%) as a colorless liquid. R_f 0.26 (25% ethyl acetate in hexanes); ^1H NMR (300 MHz, CDCl_3) δ 5.91 (m, 1H, $\text{CH}_2=\text{CH}-$), 5.34 (m, 1H, $\text{CH}_2=\text{CH}-$), 5.26 (m, 1H, $\text{CH}_2=\text{CH}$), 4.64 (dt, 2H, J = 5.6, ~1 Hz, $\text{CH}_2=\text{CHCH}_2$), 4.58 (t, 1H, J = 5.3 Hz, $\text{CH}(\text{OCH}_3)_2$), 4.17 (d, 2H, J = 5.3 Hz, $\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 3.46 (s, 2H, CH_2), 3.39 (s, 6H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 165.9, 131.5, 118.7, 101.0, 66.0, 63.8, 53.9, 41.2; FTIR (neat film) 2955 (m), 1757 (s), 1738 (s), 1447 (m), 1412 (m), 1367 (s), 1340 (s), 1323 (s), 1276 (s), 1193 (s), 1134 (s), 1102 (s), 1078 (s), 1046 (s) cm^{-1} ; HRMS (Cl $^+$) m/z : Calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_6$ ($\text{M}+\text{NH}_4$) $^+$ 250.1291, found 250.1296.



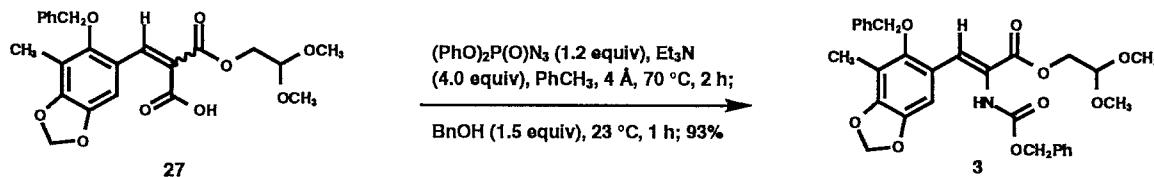
α,β -Unsaturated Diester 2 To a mixture of aldehyde **20** (3.84 g, 14.2 mmol, 1.1 equiv), **26** (3.00 g, 12.9 mmol, 1 equiv), piperidine (2.80 mL, 28.4 mmol, 2.0 equiv), and crushed activated 3 Å molecular sieves (~6 g) in benzene (40 mL) was added dropwise glacial acetic acid (3.25 mL, 56.8 mmol, 4.0 equiv), and the resulting suspension was stirred at 23 °C for 18 h. The reaction was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution: 20 → 33% ethyl acetate in hexanes) to afford **2** (6.20 g, 99%) as an inseparable mixture of *E/Z* isomers (1.3:1). R_f 0.62 (10% ethyl ether in dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ major isomer: 8.07 (s, 1H, ArCH), 7.38 (m, 5H, Ph–H), 6.83 (s, 1H, ArH), 5.98 (s, 2H, ArOCH_2OAr), 5.75 (m, 1H, $\text{CH}_2=\text{CH}$), 5.34 (m, 1H, $\text{CH}_2=\text{CH}$), 5.24 (m, 1H, $\text{CH}_2=\text{CH}$), 4.77 (s, 2H, Bn CH_2), 4.72 (m, 2H, $\text{CH}_2=\text{CHCH}_2$), 4.64 (t, 1H, J = 5.6 Hz, $\text{CH}(\text{OCH}_3)_2$), 4.32 (d, 2H, J = 5.6 Hz, $\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 3.41 (s, 6H, OCH_3),

2.16 (s, 3H, ArCH₃), minor isomer: 8.06 (s, 1H, ArCH), 7.38 (m, 5H, Ph–H), 6.76 (s, 1H, ArH), 5.98 (s, 2H, ArOCH₂OAr), 5.73 (m, 1H, CH₂=CH), 5.38 (m, 1H, CH₂=CH), 5.28 (m, 1H, CH₂=CH), 4.77 (s, 2H, Bn CH₂), 4.78 (m, 2H, CH₂=CHCH₂), 4.59 (t, 1H, *J* = 5.6 Hz, CH(OCH₃)₂), 4.23 (d, 2H, *J* = 5.6 Hz, CH₂CH(OCH₃)₂), 3.40 (s, 6H, OCH₃), 2.16 (s, 3H, ArCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 166.2, 163.9, 163.8, 153.5, 149.5, 143.6, 139.1, 139.0, 136.3, 131.8, 131.4, 128.6, 128.4, 123.6, 119.4, 119.1, 118.2, 114.1, 104.7, 104.6, 101.7, 101.2, 101.0, 77.5, 77.4, 66.2, 65.8, 63.9, 63.8, 53.9, 53.8, 14.1, 9.3; IR (neat film) 2928 (w), 1732 (s), 1609 (m), 1476 (m), 1423 (m), 1243 (s), 1217 (s), 1186 (s), 1096 (s), 1079 (s) cm⁻¹; HRMS (FAB⁺) *m/z*: calcd for C₂₆H₂₈O₉Na (MNa⁺) 507.1631, found 507.1640.



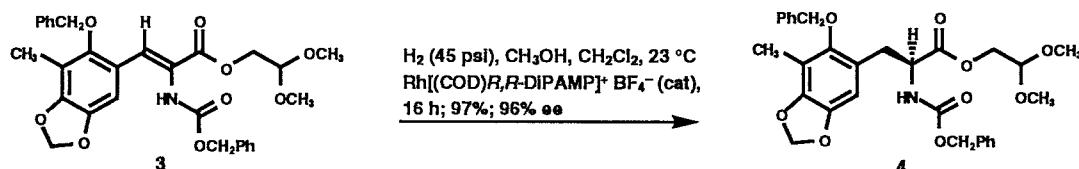
α,β-Unsaturated Acid 27. To solution of **2** (6.20 g, 12.8 mmol, 1 equiv) in tetrahydrofuran (30 mL) was added sequentially a solution of triethylammonium formate (1 M in tetrahydrofuran, 38.4 mL, 38.4 mmol, 3.0 equiv) and solid tetrakis(triphenylphosphine)palladium (120 mg), and the resulting solution was stirred at 23 °C for 4 h. All volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography (10% methyl alcohol in dichloromethane) to yield the yellow oil **27** (5.33 g 94%) as a mixture of *E/Z* isomers (4:1). *R*_f 0.21 (10% methyl alcohol in dichloromethane); ¹H NMR (500 MHz, CDCl₃) δ major isomer: 8.19 (s, 1H, ArCH), 7.40 (m, 5H, Ph–H), 6.82 (s, 1H, ArH), 6.00 (s, 2H, ArOCH₂OAr), 4.78 (s, 2H, Bn CH₂), 4.61 (t, 1H, *J* = 5.8 Hz, CH(OCH₃)₂), 4.29 (d, 2H, *J* = 5.8 Hz, CO₂CH₂), 3.40 (s, 6H, OCH₃), 2.15 (s, 3H, ArCH₃), minor isomer: 8.21 (s, 1H, ArCH), 7.40 (m, 5H, Ph–H), 7.13 (s, 1H, ArH), 5.96 (s, 2H, ArOCH₂OAr), 4.78 (s, 2H, Bn CH₂), 4.59 (t,

1H, $J = 5.8$ Hz, $CH(OCH_3)_2$), 4.24 (d, 2H, $J = 5.8$ Hz, CO_2CH_2), 3.38 (s, 6H, OCH_3), 2.15 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.9, 166.3, 164.8, 153.8, 149.9, 143.6, 143.5, 141.6, 141.4, 136.1, 135.9, 128.7, 128.5, 128.4, 128.3, 122.0, 121.5, 119.2, 119.1, 114.0, 113.8, 105.2, 104.7, 101.7, 101.0, 100.9, 77.6, 77.5, 63.9, 63.7, 53.9, 53.8, 53.3, 50.3, 9.2; IR (neat film) 3500-2500 (m), 2958 (m), 1735 (s), 1701 (s), 1608 (m), 1476 (s), 1423 (s), 1258 (s), 1218 (m), 1188 (s), 1135 (m), 1096 (s) cm^{-1} ; MS (EI $^+$) m/z : 444 (M $^+$).

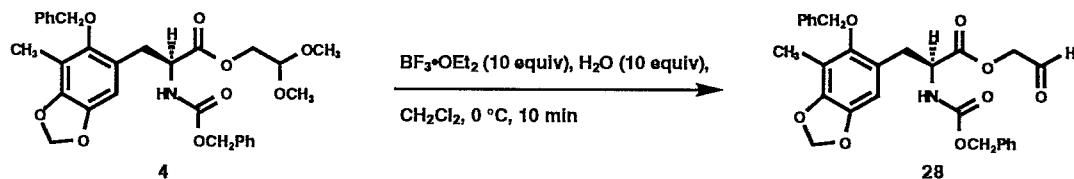


Benzyl Carbamate 3. To a mixture of **27** (5.32 g, 11.2 mmol, 1 equiv), triethylamine (6.24 mL, 44.8 mmol, 4.0 equiv), and crushed, activated 4 Å molecular sieves (~20 g) in toluene (53 mL) was added diphenylphosphoryl azide (3.10 mL, 14.4 mmol, 1.2 equiv), and the resulting suspension was heated to 70 °C for 2 h. The reaction mixture was cooled to 23 °C, and benzyl alcohol (1.73 mL, 16.8 mmol, 1.5 equiv) was then added. The suspension was stirred at 23 °C for 1 h, filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution: 20 → 50% ethyl acetate in hexanes) to afford **3** (5.90 g, 93%) as a pale yellow solid (mp 102–103 °C). R_f 0.25 (33% ethyl acetate in hexanes); 1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 1H, Ph–H & ArCH), 6.92 (s, 1H, ArH), 6.70 (s (br), 1H, NH), 5.99 (s, 2H, ArOCH₂OAr), 5.10 (s, 2H, Cbz CH₂), 4.70 (m (br), 2H, Bn CH₂), 4.58 (t (br), 1H, J = unres, $CH(OCH_3)_2$), 4.23 (d (br), 2H, J = unres, CO_2CH_2CH), 3.39 (s, 6H, OCH_3), 2.18 (s, 3H, $ArCH_3$), *Z* configuration verified by 5.8% NOE of Ar–H upon irradiation of N–H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 151.7, 148.1, 143.4, 136.3, 135.9, 128.6, 128.5, 128.4, 128.3, 128.1, 126.3, 123.6, 120.1, 113.9, 105.0, 101.5, 101.1, 67.3,

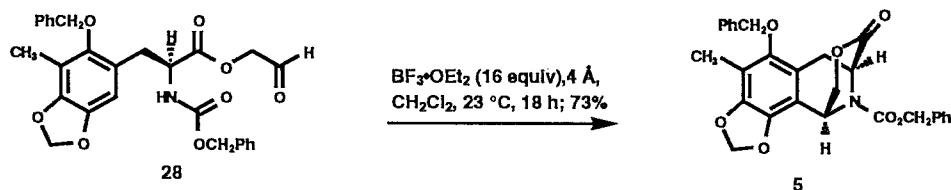
64.0, 53.9, 9.4; IR (neat film) 3350 (w, br), 2940 (w), 1718 (s), 1498 (m), 1473 (m), 1423 (m), 1247 (s), 1193 (s), 1130 (m), 1094 (s), 1069 (m) cm^{-1} ; HRMS (FAB $^{+}$) m/z : calcd for $\text{C}_{30}\text{H}_{31}\text{NO}_9\text{Na}$ (MNa^{+}) 572.1896, found 572.1909.



Protected Amino Acid 4 A solution of **3** (800 mg, 1.46 mmol, 1 equiv) and $\text{Rh}[(\text{COD})R,R\text{-DiPAMP}]^{+}\text{BF}_4^{-}$ (20 mg) in a mixture of methyl alcohol and dichloromethane (10:1 (v/v), 11.0 mL) was placed in a high pressure Parr reactor and was purged with hydrogen gas (5 x 50 psi). The reaction mixture was sealed under hydrogen (50 psi) and was stirred at 23 °C for 16 h. The solution was concentrated, and the residue was purified by flash column chromatography (gradient elution: 33 → 50% ethyl acetate in hexanes) to yield **4** (774 mg, 97%) as a white solid (mp 93.5–94.0 °C). R_f 0.25 (33% ethyl acetate in hexanes); *ee*: 96% (HPLC Chiracel OD, 10% isopropyl alcohol in hexanes); $[\alpha]_D^{23} -1.9^\circ$ ($c = 0.67$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 7.36 (m, 10H, Ph–H), 6.50 (s, 1H, ArH), 5.92 (s, 2H, ArOCH_2OAr), 5.75 (d, 1H, $J = 7.8$ Hz, NH), 5.03 (s, 2H, Cbz CH_2), 4.76 (s, 2H, Bn CH_2), 4.53 (m, 1H, CHCO_2), 4.46 (t, 1H, $J = 5.6$ Hz, $\text{CH}(\text{OCH}_3)_2$), 4.09 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}$), 3.35 (s, 6H, OCH_3), 3.06 (dd, 1H, $J = 4.7, 13.4$ Hz, ArCH_2), 2.94 (dd, 1H, $J = 7.6, 13.4$ Hz, ArCH_2), 2.20 (s, 3H, ArCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 171.3, 155.8, 150.5, 146.2, 143.3, 136.8, 136.5, 128.5, 128.4, 128.1, 127.9, 127.8, 121.2, 113.6, 107.1, 101.2, 101.1, 75.4, 66.6, 63.6, 55.2, 53.9, 53.8, 32.7, 9.7; IR (neat film) 3390 (w), 2949 (w), 1724 (s), 1500 (m), 1476 (s), 1213 (m), 1034 (m), 1091 (s), 1027 (m) cm^{-1} ; HRMS (EI $^{+}$) m/z : Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_9$ (M^{+}) 551.2153, found 551.2159.

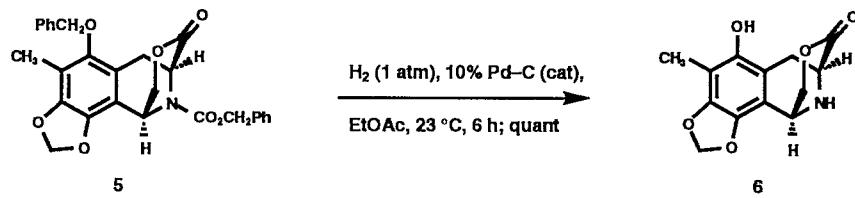


Aldehyde 28. To a solution of **4** (175 mg, 0.318 μ mol, 1 equiv) and water (57 μ L, 3.18 mmol, 10.0 equiv) in dichloromethane (10.0 mL) at 0 °C was added boron trifluoride etherate (392 μ L, 3.18 mmol, 10.0 equiv), and the resulting solution was stirred at this temperature for 10 min. The Lewis acid was neutralized with the slow addition of saturated aqueous sodium bicarbonate solution (10.0 mL), and the resulting mixture was then partitioned between saturated aqueous sodium bicarbonate solution (80 mL) and dichloromethane (40 mL). The aqueous phase was extracted further with ethyl acetate (2 x 50 mL), and the combined organic layers were dried (sodium sulfate) and concentrated to afford crude aldehyde **28** of sufficient purity. R_f 0.24 (50% ethyl acetate in hexanes); 1 H NMR (500 MHz, CDCl_3) δ 9.44 (s, 1H, CHO), 7.32 (m, 10H, Ph–H), 6.50 (s, 1H, ArH), 5.95 (s, 2H, ArOCH₂OAr), 5.72 (d, 1H, J = 7.4 Hz, NH), 5.07 (d, 1H, J = 10.7 Hz, Cbz CH₂), 5.02 (d, 1H, J = 10.7 Hz, Cbz CH₂), 4.78 (d, 1H, J = 10.2 Hz, Bn CH₂), 4.74 (d, 1H, J = 10.2 Hz, Bn CH₂), 4.58 (m, 1H, CHCO₂), 4.53 (d, 1H, J = 16.8 Hz, CH₂CHO), 4.48 (d, 1H, J = 16.8 Hz, CH₂CHO), 3.04 (m, 2H, ArCH₂), 2.20 (s, 3H, ArCH₃); IR (neat film) 3353 (w, br), 2913 (w), 1724 (s), 1476 (m), 1254 (m), 1215 (m), 1184 (m), 1090 (s), 1063 (m), 1027 (m) cm^{-1} .



Lactone 5. Boron trifluoride etherate (640 μ L, 5.20 mmol, 16.4 equiv) was added to a mixture of crude aldehyde **28** (0.318 mmol, 1 equiv) and crushed, activated 4 Å molecular sieves (2.8 g) in dichloromethane (32 mL) at 0 °C, and the resulting suspension was stirred at 23 °C for 18 h. The reaction mixture was quenched by the addition of

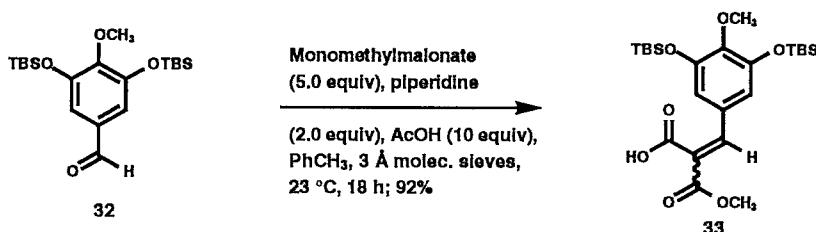
saturated aqueous sodium bicarbonate solution (100 mL), and the mixture was partitioned. The aqueous layer was further extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 0 → 5% ethyl acetate in dichloromethane) to afford **5** (113 mg, 73%) as a white solid (mp 53–55 °C). R_f 0.19 (dichloromethane); $[\alpha]_D^{23} -9.8^\circ$ (c = 0.40, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3 , 55 °C) δ 7.38 (m, 10H, Ph–H), 6.00 (s, 1H, ArOCH_2OAr), 5.97 (s, 1H, ArOCH_2OAr), 5.49 (m (br), 1H, ArCH), 5.19 (m, 3H, Cbz CH₂ & CHCO₂), 4.72 (m, 3H, Bn CH₂ & CO₂CH₂), 4.43 (d, 1H, $J = 10.4$ Hz, CO₂CH₂), 3.18 (m, 1H, ArCH₂), 2.98 (m, 1H, ArCH₂), 2.18 (s, 3H, ArCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 153.1, 149.9, 145.3, 139.3, 136.8, 135.4, 128.5, 128.4, 128.3, 128.1, 127.6, 118.5, 118.1, 114.0, 113.8, 111.5, 101.6, 74.6, 73.4, 67.9, 52.8, 52.1, 45.4, 44.5, 28.1, 27.6, 9.3; IR (neat film) 2920 (w), 1747 (s), 1710 (s), 1455 (s), 1432 (s), 1321 (m), 1299 (s), 1230 (m), 1163 (m), 1096 (s), 1058 (m), 1042 (m) cm^{-1} ; HRMS (EI⁺) m/z : calcd for $\text{C}_{28}\text{H}_{25}\text{NO}_7$ (M^+) 487.1629, found 487.1628.



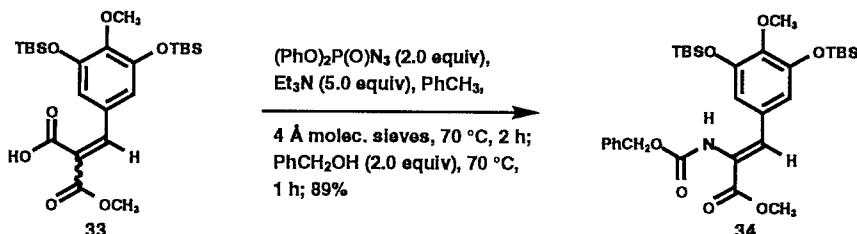
Aminophenol 6. A mixture of lactone **5** (240 mg, 0.493 mmol, 1 equiv) and 10% palladium on carbon (20 mg) in ethyl acetate (10.0 mL) was stirred under 1 atm of hydrogen at 23 °C for 6 h. The reaction mixture was filtered, and the filtrate was concentrated to afford **6** (131 mg, quant) as a colorless film. R_f 0.20 (ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 5.94 (d, 1H, $J \sim 1$ Hz, OCH₂O), 5.91 (d, 1H, $J \sim 1$ Hz, OCH₂O), 4.76 (dd, 1H, $J = 3.7, 10.6$ Hz, CH₂O₂C), 4.43 (d, 1H, $J = 10.6$ Hz, CH₂O₂C), 4.38 (d, 1H, $J = 3.7$ Hz, ArCH), 4.29 (d (br), 1H, $J = 6.2$ Hz, CHCO₂), 3.00 (dd, 1H, $J = 1.1, 16.9$ Hz, ArCH₂), 2.91 (dd, 1H, $J = 6.2, 16.9$ Hz, ArCH₂); FTIR (neat

film) 3360 (w, br), 2951 (w), 1731 (s), 1461 (s), 1432 (s), 1241 (m), 1117 (m), 1096 (s), 1076 (m), 1048 (s), 1025 (m) cm^{-1} ; HRMS (EI $^+$) m/z : Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$ (M^+) 263.0794, found 263.0802.

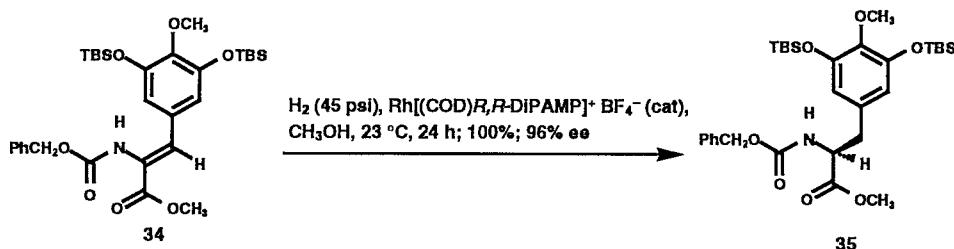
Right Fragment



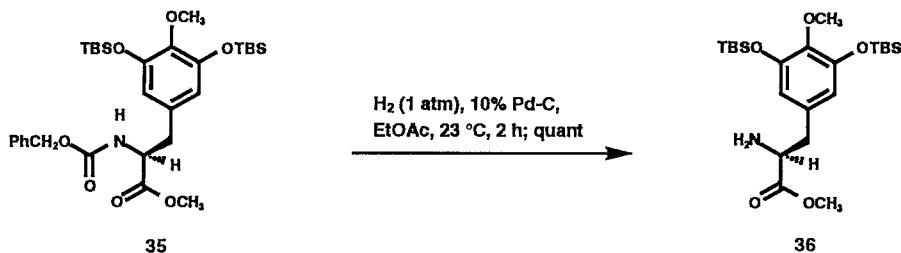
Acid 33. Piperidine (1.01 mL, 10.2 mmol, 2.0 equiv) was added to a suspension of **32** (2.02 g, 5.10 mmol, 1 equiv), monomethyl malonate (3.01 g, 25.5 mmol, 5.0 equiv), acetic acid (2.92 mL, 51.0 mmol, 10.0 equiv), and crushed, activated 3 Å molecular sieves (~12 g) in toluene (25.0 mL), and the resulting suspension was stirred at 23 °C for 18 h. The reaction mixture was filtered, washing well with ethyl acetate (100 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography (4% methyl alcohol in dichloromethane) to give acid **33** (2.32 g, 92%) as an inseparable mixture of *E/Z* isomers. R_f 0.42 (10% methyl alcohol in dichloromethane); ^1H NMR (500 MHz, CDCl_3) δ (major isomer) 7.71 (s, 1H, ArCH), 6.83 (s, 2H, ArH), 3.90 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.00 (s, 18H, *t*-butyl), 0.18 (s, 12H, SiCH_3), δ (minor isomer) 7.71 (s, 1H, ArCH), 6.65 (s, 2H, ArH), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 1.00 (s, 18H, *t*-butyl), 0.18 (s, 12H, SiCH_3); ^{13}C NMR (126 MHz, CDCl_3) δ 169.9, 165.3, 150.0, 145.8, 144.5, 127.4, 122.5, 116.8, 60.0, 52.8, 25.6, 18.2, -4.7; IR (neat film) 3600-2600 (m, br), 2955 (s), 1741 (s), 1713 (s), 1569 (s), 1493 (s), 1253 (s), 1219 (m), 1096 (s), 864 (s) cm^{-1} ; HRMS (FAB $^-$) m/z : Calcd for $\text{C}_{24}\text{H}_{39}\text{O}_7\text{Si}_2$ (M^-) 495.2234, found 495.2253.



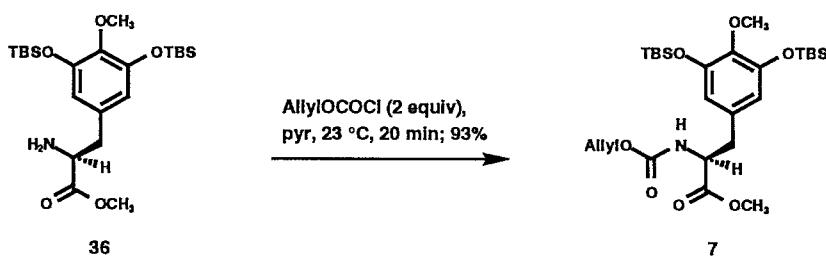
Benzyl Carbamate 34. To a suspension of **33** (3.35 g, 6.75 mmol, 1 equiv), triethylamine (4.71 mL, 33.8 mmol, 5.0 equiv), and crushed, activated 3 Å molecular sieves (~15 g) in toluene (50 mL) was added diphenylphosphoryl azide (2.90 mL, 13.5 mmol, 2.0 equiv), and the resulting suspension was heated at 70 °C for 2 h. Benzyl alcohol (1.40 mL, 13.5 mmol, 2.0 equiv) then was added to the reaction mixture, and the suspension was stirred at 70 °C for 1 h. The reaction was filtered, washing well with ethyl acetate (100 mL), and the filtrate was concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) to afford **34** as a pale yellow oil (3.62 g, 89%). R_f 0.53 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, CDCl_3) δ 7.34 (m, 5H, Cbz ArH), 7.18 (s, 1H, ArCH), 6.77 (s, 2H, ArH), 6.14 (s (br), 1H, NH), 5.13 (s, 2H, Cbz CH_2), 3.81 (s (br), 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.00 (s, 18H, *t*-butyl), 0.16 (s, 12H, SiCH_3), *Z* configuration verified by 11.6% NOE of ArH's upon irradiation of NH; ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 149.8, 144.4, 135.8, 132.5, 130.0, 128.5, 128.4, 128.2, 126.1, 123.4, 120.2, 116.4, 67.6, 60.0, 52.5, 25.7, 18.3, -4.7; IR (neat film) 3500 (w, br), 2951 (m), 1723 (s), 1567 (m), 1493 (s), 1424 (m), 1289 (s), 1259 (s), 1122 (s), 1006 (w), 829 (s) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{31}\text{H}_{48}\text{NO}_7\text{Si}_2$ (MH^+) 602.2969, found 602.2993.



Protected Aminoacid 35. A solution of **34** (6.00 g, 9.98 mmol, 1 equiv) and $\text{Rh}[(\text{COD})R,R\text{-DiPAMP}]^+\text{BF}_4^-$ (75 mg) in a mixture of methyl alcohol and dichloromethane (10:1 (v/v), 110 mL) was placed in a high pressure Parr reactor and was purged with hydrogen gas (5 x 50 psi). The reaction mixture was sealed under hydrogen (50 psi) and was stirred at 23 °C for 24 h. The solution was concentrated, and the residue was purified by flash column chromatography (2.5% ethyl acetate in dichloromethane) to yield **35** (6.01 g, quant) as a colorless viscous oil. R_f 0.41 (20% ethyl acetate in hexane); *ee*: 96% (HPLC ChirPak AD, 1% isopropyl alcohol in hexanes); $[\alpha]_D^{23} +30.5^\circ$ ($c = 0.40$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.32 (m, 5H, Cbz ArH), 6.23 (s, 2H, ArH), 5.18 (d, 1H, $J = 8.0$ Hz, NH), 5.12 (d, 1H, $J = 12.3$ Hz, Cbz CH_2), 5.07 (d, 1H, $J = 12.3$ Hz, Cbz CH_2), 4.59 (m, 1H, Ar CH_2CH), 3.72 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 2.95 (d, 2H, $J = 5.3$ Hz, Ar CH_2), 0.98 (s, 18H, *t*-butyl), 0.15 (s, 12H, SiCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 155.6, 149.8, 142.1, 136.2, 130.5, 128.5, 128.1, 115.6, 67.0, 59.9, 54.5, 52.2, 37.6, 25.7, 18.3, -4.7; IR (neat film) 3350 (w, br), 2931 (m), 2858 (w), 1728 (s), 1577 (m), 1496 (s), 1434 (s), 1360 (m), 1253 (s), 1230 (s), 1209 (m), 1091 (s), 831 (s) cm^{-1} ; HRMS (FAB⁺) *m/z*: Calcd for C₃₁H₅₀NO₇Si₂ (MH⁺) 604.3126, found 604.3103.

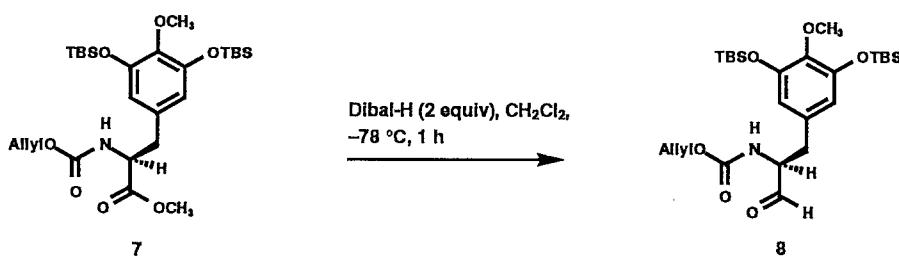


Amino Ester 36. A solution of **35** (1.00 g, 1.66 mmol, 1 equiv) and 10% palladium on activated charcoal (50 mg) in ethyl acetate (40 mL) was stirred under 1 atm of hydrogen gas at 23 °C for 2 h. The reaction mixture was gravity filtered, and the filtrate was concentrated to afford **36** (780 mg, quant) as a viscous oil. R_f 0.38 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +5.7^\circ$ ($c = 0.70$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.35 (s, 2H, ArH), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.67 (dd, 1H, $J = 5.4, 7.9$ Hz, CHCO_2CH_3), 2.92 (dd, 1H, $J = 5.4, 13.5$ Hz, ArCH₂), 2.71 (dd, 1H, $J = 7.9, 13.5$ Hz, ArCH₂), 1.00 (s, 9H, *t*-butyl), 0.19 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 175.2, 149.6, 141.7, 132.1, 115.5, 59.8, 55.6, 51.9, 40.5, 25.6, -4.7; FTIR (neat film) 2955 (m), 2930 (m), 2858 (m), 1743 (s), 1577 (s), 1495 (m), 1433 (m), 1356 (m), 1252 (m), 1229 (m), 1087 (s), 858 (s) cm^{-1} ; HRMS (FAB⁺) m/z : Calcd for $\text{C}_{23}\text{H}_{43}\text{NO}_5\text{Si}_2\text{Na}$ (MNa^+) 492.2578, Found 492.2580.



Allyl Carbamate 7. To a solution of **36** (780 mg, 1.66 mmol, 1 equiv) in pyridine (8 mL) at 0 °C was added dropwise allylchloroformate (352 μL , 3.32 mmol, 2.0 equiv), and the reaction was stirred at 23 °C for 20 min. The mixture was concentrated at 23 °C and the residue was partitioned between water (50 mL) and dichloromethane (3 x 25 mL). The combined organic layers was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (15% ethyl acetate in hexane) to give

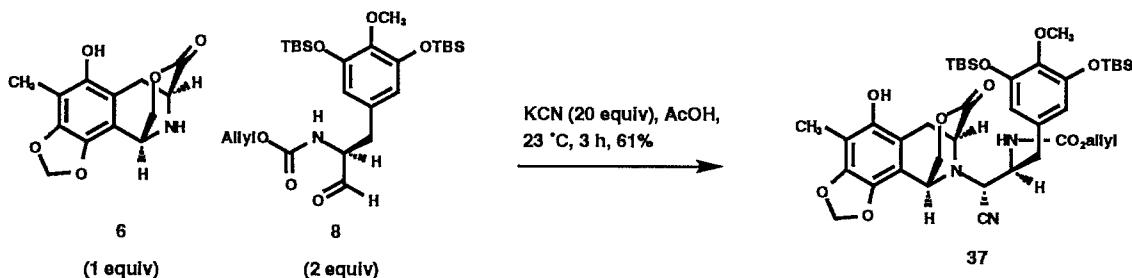
7 (856 mg, 93%) as a colorles oil. R_f 0.37 (20% ethyl acetate in hexane); $[\alpha]_D^{23} +26.2^\circ$ ($c = 0.40$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 6.28 (s, 2H, ArH), 5.89 (m, 1H, vinyl H), 5.28 (d, 1H, $J = 17.3$ Hz, vinyl H), 5.20 (d, 1H, $J = 10.5$ Hz, vinyl H), 5.14 (d, 1H, $J = 7.9$ Hz, NH), 4.35 (m, 3H, allylic CH_2 and CHCOCH_3), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 2.94 (d, 2H, $J = 9.4$ Hz, ArCH_2), 1.00 (s, 9H, *t*-butyl), 0.19 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 149.8, 132.6, 130.6, 117.8, 115.6, 65.8, 59.9, 54.5, 52.3, 37.5, 25.7, 18.3, -4.7; FTIR (neat film) 3280 (w, br), 2955 (s), 2931 (s), 2858 (s), 1737 (s), 1716 (s), 1578 (s), 1519 (s), 1472 (s), 1361 (m), 1253 (s), 1229 (s), 1207 (m), 1092 (s), 1011 (m), 832 (s) cm^{-1} ; HRMS (FAB $^+$) *m/z*: Calcd for $\text{C}_{27}\text{H}_{47}\text{NO}_7\text{Si}_2\text{Na}$ (MNa^+) 576.2789, Found 576.2777.



Aldehyde 8. To a solution of **7** (850 mg, 1.54 mmol, 1 equiv) in dichloromethane (85 mL) at -78°C was added diisobutylaluminun hydride (1.5 M in toluene, 2.05 mL, 3.08 mmol, 2.0 equiv), and the reaction mixture was stirred at -78°C for 1 h. Excess reducing agent was quenched by the sequential addition of methyl alcohol (700 μL), sodium sulfate decahydrate (~ 5 g), and celite (~ 2 g). The mixture was stirred at 23 $^\circ\text{C}$ for 1 h, and was then filtered through a pad of celite. The filtrate was concentrated and the residue was dissolved in diethyl ether (150 mL). The solution was again filtered through a pad of celite, and the filtrate was concentrated to give the crude aldehyde **8**, which was used immediately without further purification in the coupling reaction with **6**. R_f 0.33 (25% ethyl acetate in hexanes); ^1H NMR crude product (400 MHz, CDCl_3) δ 9.61 (s, 1H, CHO), 6.28 (s, 2H, ArH), 5.90 (m, 1H, vinyl H), 5.30 (dd, 1H, $J = 1.2, 17.2$ Hz, vinyl H), 5.21 (m, 2H, vinyl H, NH), 4.58 (m, 2H, allyl H), 4.41 (m, 1H,

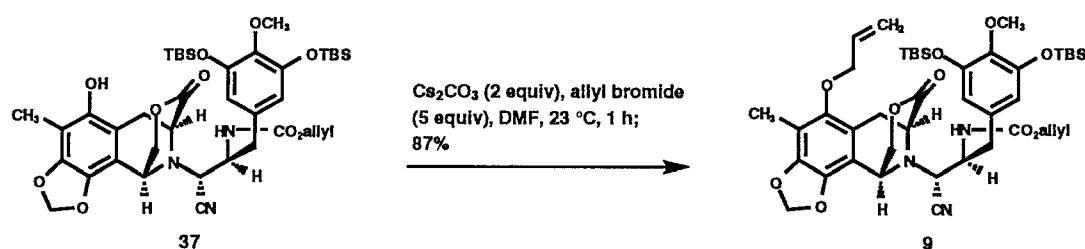
*CHCHO), 3.70 (s, 3H, OCH₃), 3.01 (dd, 1H, *J* = 6.0, 14.4 Hz, ArCH₂), 2.94 (dd, 1H, *J* = 6.8, 14.4 Hz, ArCH₂), 0.99 (s, 18H, Si-*t*-butyl), 0.15 (s, 12H, SiCH₃).*

Synthesis of the Pentacycle



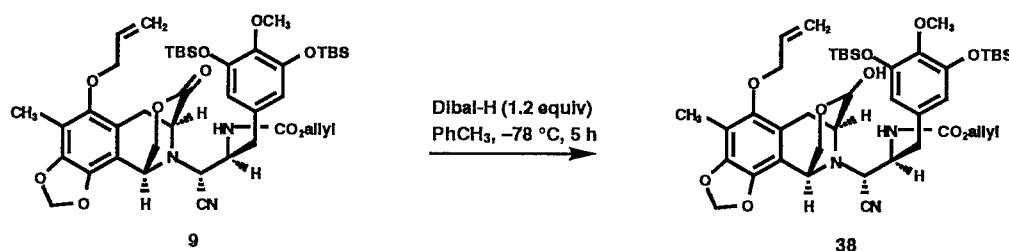
Aminonitrile 37. To a solution of amine **6** (123 mg, 0.467 mmol, 1 equiv) and crude aldehyde **8** (489 mg, 0.935 mmol, 2.0 equiv) in glacial acetic acid (5 mL) was added solid potassium cyanide (608 mg, 9.35 mmol, 20 equiv), and the resulting mixture was stirred at 23 °C for 1 h. The reaction mixture was diluted with ethyl acetate (80 mL) and was washed sequentially with saturated aqueous sodium bicarbonate solution (3 x 60 mL) and saturated aqueous sodium chloride solution (60 mL). The organic layer was dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 15% → 20% ethyl acetate in hexane) to afford **37** (159 mg) and its aminonitrile epimer (67 mg) in separate fractions (61% total). **37**: *R*_f 0.19 (25% ethyl acetate in hexane); [α]_D²³ -36.8° (c = 1.30, CH₂Cl₂); ¹HNMR (400 MHz, CDCl₃) δ (multiple and broadened resonances due to carbamate rotamers at 23 °C) 6.34 (s, ArH), 6.32 (s, ArH), 6.30 (s, ArH), 5.98–5.80 (m, vinyl H and OCH₂O), 5.33 (m), 5.28 (m), 5.23 (m), 5.2–4.8 (m (br)), 4.63 (m), 4.57 (m), 4.45 (m (br)), 4.40–4.25 (m) 4.10 (m (br)), 3.93 (m (br)), 3.70 (s, OCH₃), 3.61 (s, OCH₃), 2.13 (s, ArCH₃), 2.08 (s, ArCH₃), 1.00 (s, *t*-butyl), 0.99 (s, *t*-butyl), 0.19 (s, Si(CH₃)₂), 0.11 (s, Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 169.7, 169.2, 156.1, 155.5, 150.1, 150.0, 146.3, 145.1, 142.2, 142.0, 137.9, 132.3, 132.1, 131.3, 130.7, 118.1, 117.9, 117.8, 115.9, 115.5, 115.4, 115.2, 115.0, 110.1, 109.7, 108.9, 107.3, 101.4, 101.3, 73.7, 73.4,

66.0, 60.4, 59.9, 59.8, 57.1, 57.0, 55.2, 55.0, 52.0, 50.7, 47.9, 46.7, 38.2, 35.1, 31.6, 25.7, 22.9, 22.6, 22.0, 21.0, 18.3, 14.1, 8.7, 8.6, -4.7, -4.8; FTIR (neat film) 3300 (m, br), 2955 (s), 2932 (s), 2858 (s), 1727 (s), 1712 (s), 1578 (m), 1495 (m), 1434 (s), 1360 (m), 1255 (s), 1233 (s), 1095 (s), 1043 (m), 1009 (s), 860 (s), 832 (s) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{40}\text{H}_{58}\text{N}_3\text{O}_{10}\text{Si}_2$ (MH^+) 796.3661, Found 796.3636.

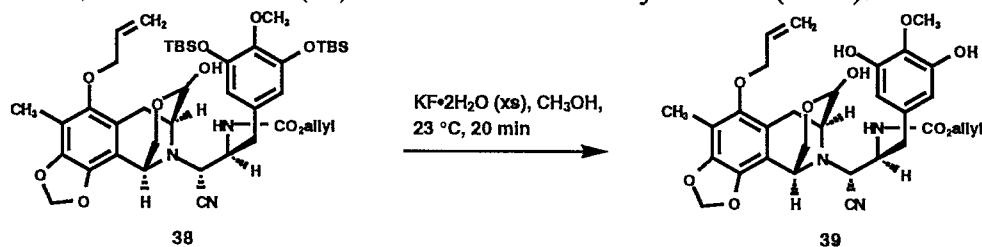


Allyl Ether 9. To a solution of aminonitrile **37** (986 mg, 1.24 mmol, 1 equiv) in DMF (10 mL) was added sequentially flame-dried cesium carbonate (809 mg, 2.78 mmol, 2.0 equiv) and allyl bromide (537 μL , 6.20 mmol, 5.0 equiv), and the mixture was stirred at 23 °C for 1 h. Excess base was neutralized with the addition of acetic acid (4 mL), and the mixture was then partitioned between saturated aqueous sodium bicarbonate solution (100 mL) and dichloromethane (2 x 50 mL). The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford **9** (901 mg, 87%) as a colorless film. R_f 0.41 (25% ethyl acetate in hexane); $[\alpha]_D^{23} -40.0^\circ$ ($c = 0.53, \text{CH}_2\text{Cl}_2$); ^1H NMR (500 MHz, CDCl_3) δ (multiple and broadened resonances due to carbamate rotamers at 23 °C) 6.32 (s, ArH), 6.29 (s, ArH), 6.1–5.7 (m, vinyl H and OCH_2O), 5.41 (m, vinyl H), 5.29 (m, vinyl H), 5.31 (m, vinyl H), 5.30–5.10 (m), 4.93 (m (br)), 4.79 (m (br)), 4.70–4.05 (m), 3.91 (m (br)), 3.70 (s, OCH_3), 3.60 (s, OCH_3), 3.42 (m), 3.19 (m), 3.04–2.89 (m), 2.64 (m), 2.17 (s, ArCH_3), 2.10 (s, ArCH_3), 1.01 (s, *t*-butyl), 0.98 (s, *t*-butyl), 0.18 (s, $\text{Si}(\text{CH}_3)_2$), 0.11 (s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 168.8, 156.1, 155.4, 150.1, 150.0, 149.9, 149.7, 145.4, 145.3, 142.2, 142.0, 140.4, 140.2, 133.4, 133.3, 132.4,

132.1, 131.3, 130.8, 118.1, 117.9, 117.6, 117.5, 117.1, 116.0, 115.4, 115.2, 115.0, 114.1, 113.8, 109.8, 109.2, 101.7, 101.6, 73.6, 73.5, 73.2, 66.0, 59.9, 59.8, 57.2, 56.9, 55.3, 54.9, 53.4, 52.1, 50.6, 48.2, 46.8, 38.1, 35.13, 25.7, 25.6, 23.5, 22.5, 18.3, 9.4, 9.3, -4.7, -4.8; FTIR (neat film) 3300 (w, br), 2955 (m), 2932 (s), 2858 (m), 1727 (s), 1577 (m), 1494 (m), 1461 (s), 1434 (m), 1253 (s), 1232 (s), 1095 (s), 1043 (m), 1009 (m), 860 (m), 832 (s) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{43}\text{H}_{61}\text{N}_3\text{O}_{10}\text{Si}_2\text{Na}$ (MNa^+) 858.3793, found 858.3820.

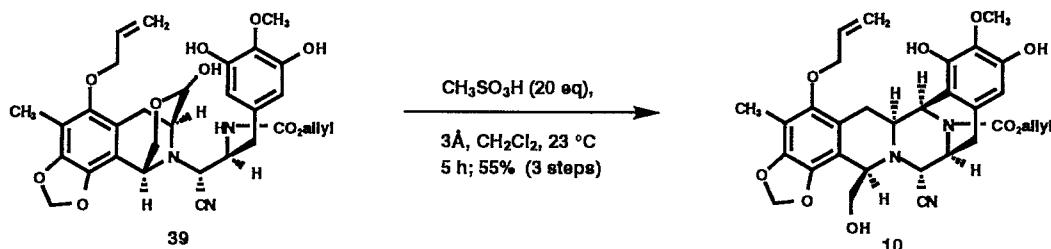


Triol 10. To a solution of **9** (390 mg, 0.467 mmol, 1 equiv) in a solution of toluene (50 mL) at -78°C was added a solution of diisobutylaluminum hydride (1.5 M in toluene, 374 μL , 0.560 mmol, 1.2 equiv), and the resulting solution was stirred at -78°C for 5 h. Excess reducing agent was quenched by the slow sequential addition of methyl alcohol (500 μL), sodium sulfate decahydrate (~ 5 g), and celite at -78°C . The suspension was stirred at 23°C for 1 h before it was filtered through a pad of celite. The filtrate was concentrated, and the residue (**38**) was dissolved in methyl alcohol (4 mL).



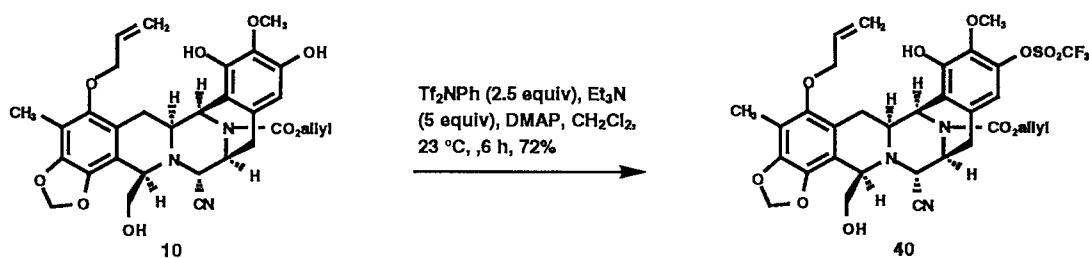
To this solution was added potassium fluoride dihydrate (250 mg, 2.66 mmol, 5.7 equiv), and the reaction was stirred at 23°C for 20 min. The mixture was partitioned between dichloromethane (50 mL) and 80% saturated aqueous sodium chloride solution (80 mL), and the aqueous phase was further extracted with ethyl acetate (2 x 50 mL). The

combined organic layers were dried (sodium sulfate) and concentrated, and the residue (**39**) was dissolved in dichloromethane (100 mL).



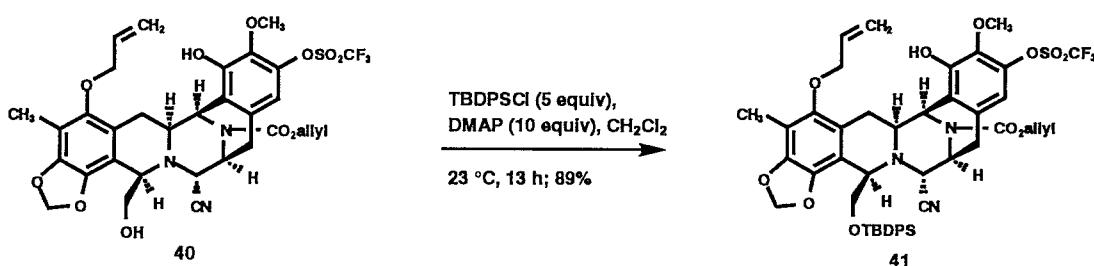
To this solution was added crushed, flamed 3 Å molecular sieves (6.20 g) followed by methanesulfonic acid (531 μL , 8.21 mmol, 20 equiv), and the suspension was stirred at 23 $^\circ\text{C}$ for 5 h. Excess acid was quenched by the addition of pyridine (1.32 mL, 16.4 mmol, 40 equiv), and the mixture was suction filtered, washing well 10% isopropyl alcohol in dichloromethane (4 \times 20 mL). The product solution was washed with saturated aqueous sodium chloride solution (150 mL), and the aqueous layer was further extracted with ethyl acetate (2 \times 100 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 60% \rightarrow 100% ethyl acetate in hexane) to afford triol **10** (152 mg, 55%, 3 steps) as a colorless oil. R_f 0.23 (66% ethyl acetate in hexane); $[\alpha]_D^{23} -4.4^\circ$ ($c = 0.48$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ (multiple and broadened resonances due to carbamate rotamers at 23 $^\circ\text{C}$) 6.32 (s, 1H, ArH), 6.31 (s, 1H, ArH), 6.29 (m, 1H, vinyl H), 5.90 (m, vinyl H, OCH_2O), 5.60 (s (br), ArOH), 5.50 (s (br), ArOH), 5.42 (m, 1H), 5.39 (m, 1H), 5.32-5.17 (m), 4.91 (m, 1H), 4.83 (m, 1H), 4.62 (m), 4.20 (m), 4.31 (m, 1H), 3.97 (m, 2H), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.66-3.20 (m), 2.74 (m, 1H, ArCH_2), 2.12 (s, 3H, ArCH_3), 0.87 (m, 1H, ArCH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 154.4, 153.9, 148.7, 148.6, 148.4, 146.2, 145.9, 145.5, 144.6, 144.5, 139.0, 133.7, 133.6, 132.6, 132.3, 132.0, 130.8, 130.4, 121.3, 120.6, 120.4, 118.8, 118.0, 117.9, 117.8, 117.5, 117.2, 116.3, 116.1, 115.9, 113.7, 112.5, 113.3, 112.1, 107.7, 107.2, 106.6, 101.2, 74.4, 74.1, 66.8, 66.5, 64.3, 60.9, 60.4, 59.0, 58.9, 58.2, 56.6, 52.9, 51.4, 49.8, 49.4, 48.9, 46.6, 31.0, 30.6, 30.4, 25.9, 21.0, 14.1, 9.3; FTIR (neat

film) 3300 (m, br), 2902 (m), 1686 (s), 1460 (s), 1432 (s), 1372 (m), 1328 (m), 1291 (m), 1264 (w), 1106 (s), 1064 (m), 1027 (m), 954 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_9\text{Na}$ (MNa^+) 614.2114, found 614.2133.



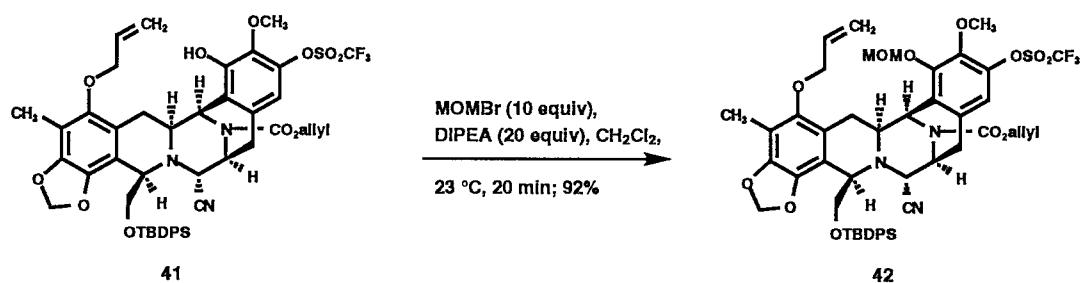
Aryl Triflate 40. To a solution of **10** (150 mg, 0.253 mmol, 1 equiv) and triethylamine (177 μL , 1.27 mmol, 5.0 equiv) in dichloromethane (15 mL) was added sequentially *N*-phenyltriflimide (227 mg, 0.634 mmol, 2.5 equiv) and DMAP (1 mg), and the reaction was stirred at 23 $^\circ\text{C}$ for 6.5 h. Excess base was neutralized by the addition of acetic acid (145 μL , 2.53 mmol, 10 equiv) followed by pyridine (306 μL , 3.79 mmol, 15 equiv). The mixture was partitioned between dichloromethane (50 mL) and saturated aqueous sodium chloride solution (80 mL), and the aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (60% ethyl acetate in hexane) to afford **40** (132 mg, 72%) as a colorless film. R_f 0.44 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +32.3^\circ$ ($c = 0.60, \text{CH}_2\text{Cl}_2$); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (signals broadened due to carbamate rotamers at 23 $^\circ\text{C}$) 6.65 (s, 1H, ArH), 6.10 (m, 1H, vinyl H), 5.92 (m, vinyl H and OCH_2O), 5.68 (s, ArOH), 5.57 (s (br)), 5.40 (m), 5.26 (m, vinyl H), 4.93 (m), 4.87 (m), 4.63 (m), 4.21 (m), 3.98 (m), 3.92 (s, 3H, OCH_3), 3.7–3.4 (m), 3.30 (m), 2.86 (m), 2.13 (s, 3H, ArCH_3), 1.81 (m, 1H, ArCH); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 154.1, 153.9, 148.7, 148.5, 147.2, 146.6, 144.8, 144.7, 141.1, 140.9, 139.1, 138.9, 136.9, 136.7, 134.2, 133.7, 132.2, 132.1, 131.7, 129.4, 127.1, 123.2, 122.3, 121.3, 121.2, 120.1, 119.9, 119.8, 118.2, 17.6, 117.5, 117.2, 116.2, 116.1, 112.8, 112.7, 112.3, 112.2, 112.1, 101.2, 74.4, 66.9, 66.7, 65.6, 65.4, 61.9,

59.5, 59.4, 58.5, 56.5, 49.7, 49.2, 48.9, 48.3, 30.9, 30.3, 25.9, 14.1, 9.3; FTIR (neat film): 3350 (w, br), 2928 (w), 1694 (s), 1685 (s), 1451 (s), 1422 (s), 1319 (m), 1257 (s), 1214 (s), 1138 (s), 1102 (s), 1026 (s), 989 (m) cm^{-1} ; HRMS (FAB $^{+}$) m/z : Calcd for $\text{C}_{32}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_{11}\text{SNa}$ (MNa^{+}) 746.1607, found 746.1616.



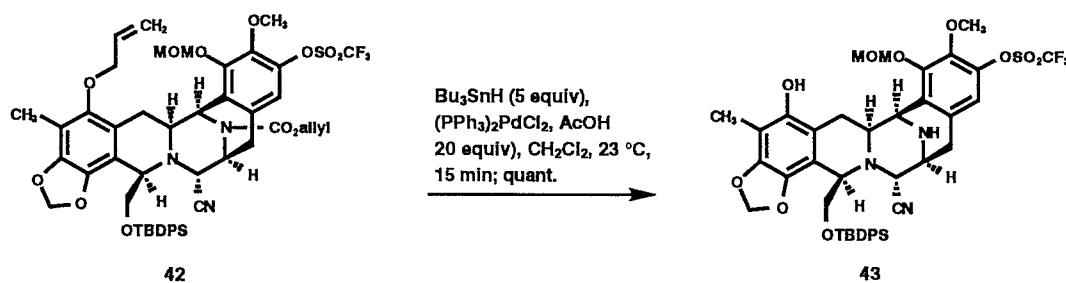
Silyl Ether 41. To a solution of **41** (90 mg, 0.124 mmol, 1 equiv) and DMAP (152 mg, 1.24 mmol, 10 equiv) in dichloromethane (10 mL) was added *t*-butyldiphenylsilylchloride (162 μL , 0.622 mmol, 5.0 equiv), and the solution was stirred at 23 °C for 13 h. The excess base was quenched by the addition of acetic acid (150 μL), and the mixture was partitioned between water (50 mL), and dichloromethane (3 x 30 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 25% \rightarrow 50% ethyl acetate in hexane) to afford **41** (106 mg, 89%) as a colorless glassy solid. R_f 0.66 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +45.2^\circ$ ($c = 1.00$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ (multiple and broadened resonances due to carbamate rotamers at 23 °C) 5.70 (m, 1H, ArH), 7.56 (m, ArH), 7.45–7.15 (m, ArH), 6.58 (m, 1H, ArH), 6.06 (m, 1H, vinyl H), 5.90 (m, 1H, vinyl H), 5.80 (s, 1H, OCH_2O), 5.13 (m, 2H, ArOH and OCH_2O), 5.4–5.1 (m), 4.92 (m), 4.83 (m), 4.61 (m), 4.20 (m), 4.09 (m), 3.92 (s, 3H, OCH_3), 3.7–3.2 (m), 2.98 (m, 1H, ArCH), 2.11 (s, 3H, ArCH $_3$), 1.90 (m, 1H, ArCH), 1.01 (s, *t*-butyl), 1.00 (s, *t*-butyl); ^{13}C NMR (126 MHz, CDCl_3) δ 171.2, 154.2, 148.6, 148.5, 147.4, 146.7, 144.6, 144.4, 141.3, 141.2, 139.3, 139.1, 136.6, 136.4, 135.7, 135.3, 134.8, 133.8, 133.0, 132.5, 132.4, 129.8, 129.7, 127.7, 122.2, 122.1, 120.5, 120.4, 119.9, 118.2, 117.6, 117.5, 117.3, 117.2, 116.9, 116.7, 112.7, 112.4, 112.1, 111.8, 101.0,

74.4, 69.3, 68.8, 66.8, 66.5, 65.3, 61.9, 60.5, 60.4, 60.3, 59.3, 56.6, 49.8, 49.2, 48.9, 48.3, 31.6, 30.7, 30.0, 26.8, 26.5, 26.2, 26.1, 22.6, 21.0, 19.0, 14.2, 14.1, 9.3, 9.2; FTIR (neat film) 3350 (w, br), 2951 (m), 1694 (s), 1458 (m), 1451 (s), 1425 (s), 1317 (m), 1257 (m), 1214 (s), 1139 (s), 1110 (s), 1038 (m), 989 (m), 824 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{48}\text{H}_{50}\text{F}_3\text{N}_3\text{O}_{11}\text{SSiNa}$ (MNa^+) 984.2785, found 984.2771.



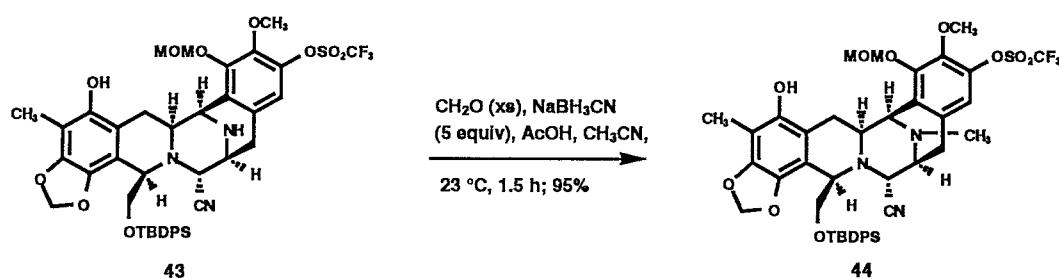
Methoxymethyl Ether 42. To a solution of **41** (94 mg, 0.0978 mmol, 1 equiv) and diisopropylethylamine (340 μ L, 1.96 mmol, 20 equiv) in dichloromethane (6 mL) at 0 $^{\circ}$ C was added bromomethylmethyl ether (80 μ L, 0.978 mmol, 10 equiv), and the solution was stirred at 23 $^{\circ}$ C for 20 min. After the reaction was quenched with methyl alcohol (100 μ L), the mixture was partitioned between saturated aqueous sodium bicarbonate solution (30 mL), and dichloromethane (2 x 30 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexane) to afford **42** (90 mg, 92%) as a colorless film. R_f 0.66 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +57.0$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ (multiple and broadened resonances due to carbamate rotamers at 23 $^{\circ}$ C) 7.6–7.1 (m, 10H, ArH), 6.74 (s, 1H, ArH), 6.10 (m, 1H, vinyl H), 5.93 (m, 1H, vinyl H), 5.81 (s, 1H, OCH_2O), 5.65 (s, 1H, OCH_2O), 5.45–5.13 (m, vinyl H, and OCH_2O), 4.91 (m, 1H), 4.69 (m, 1H), 4.59 (m, 2H), 4.16 (m, 2H), 4.07 (m, 1H), 3.87 (m, 3H, OCH_3), 3.73–3.60 (m, 4H, OCH_3 and CHOSi), 3.4–3.2 (m, 3H, CHOSi and ArCH), 2.97 (m, 1H, ArCH₂), 2.12 (s, 3H, ArCH₃), 1.83 (m, 1H, ArCH₂), 0.97 (m, 9H, *t*-butyl); ^{13}C NMR (100 MHz, CDCl_3) δ 154.1, 153.9, 148.5, 147.9, 144.6, 142.6, 142.4, 142.1, 139.3, 139.2, 135.7, 135.3, 134.8, 133.7, 132.9, 132.5, 132.4, 132.3,

129.8, 128.8, 128.7, 127.7, 120.3, 120.1, 118.5, 118.1, 117.5, 117.1, 116.7, 116.6, 116.5, 112.5, 112.4, 112.0, 111.8, 101.1, 99.7, 74.2, 69.2, 68.8, 67.0, 66.7, 61.1, 60.4, 60.2, 59.2, 58.4, 58.1, 56.5, 50.2, 49.3, 49.2, 48.3, 30.7, 30.1, 29.7, 26.8, 26.1, 26.0, 19.0, 9.2; FTIR (neat film) 2959 (m), 1709 (s), 1426 (s), 1315 (m), 1253 (m), 1213 (s), 1140 (s), 1110 (s), 1066 (s), 1015 (s), 987 (s), 921 (s), 825 (m) cm^{-1} ; MS (FAB $^{+}$) m/z : Calcd for $\text{C}_{50}\text{H}_{54}\text{F}_3\text{N}_3\text{O}_{12}\text{SSiNa}$ (MNa^{+}) 1028, found 1028.



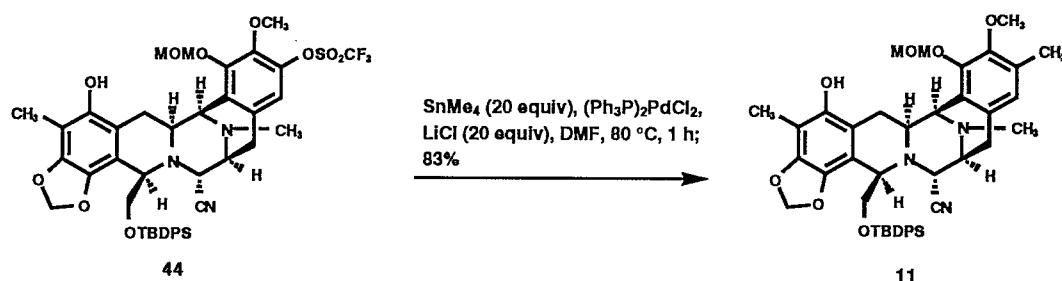
Aminophenol 43. To a solution of **42** (90 mg, 0.0895 mmol, 1 equiv), acetic acid (102 μ L, 1.79 mmol, 20 equiv), and dichlorobis(triphenylphosphine) palladium (5 mg) in dichloromethane (4 mL) was added tributyltin hydride (120 μ L, 0.448 mmol, 5.0 equiv), and the yellow/brown solution was stirred at 23 °C for 15 min. The mixture was loaded onto a silica gel column, and the product was purified by flash column chromatography (gradient elution: 50% ethyl acetate in hexane → 100% ethyl acetate) to afford **43** (79 mg, quant) as a colorless film. R_f 0.30 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +34.0$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.59 (d, 2H, $J = 9.4$ Hz, ArH), 7.5–7.2 (m, 8H, ArH), 6.76 (s, 1H, ArH), 5.75 (s, 1H, OCH_2O), 5.61 (s, 1H, OCH_2O), 5.39 (d, 1H, $J = 5.3$ Hz, OCH_2O), 5.22 (d, 1H, $J = 5.3$ Hz, OCH_2O), 5.14 (s, 1H, ArOH), 4.60 (d, 1H, $J = 1.1$ Hz, ArCH), 4.49 (d, 1H, $J = 2.3$ Hz, CHCN), 4.07 (m, 1H, ArCH), 3.85 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.75–3.40 (m (br)), 3.35 (dd, 1H, $J = 7.6$, 10.2 Hz, CHOSi), 3.28 (dd, 1H, $J = \sim 1$, 10.2 Hz, CHOSi), 3.13 (m, 2H, ArCH₂), 2.94 (d, 1H, $J = 15.9$ Hz, ArCH₂), 2.07 (s, 3H, ArCH₃), 1.77 (dd, 1H, $J = 11.0$, 13.6 Hz, ArCH₂), 0.95 (s, 9H, *t*-butyl); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 171.2, 148.4, 145.2, 144.5, 142.0, 141.2, 136.6, 135.6, 135.3, 133.0, 132.9, 132.6, 130.8,

129.7, 127.6, 120.2, 117.9, 117.1, 116.5, 112.4, 111.7, 106.0, 100.6, 99.9, 77.2, 69.2, 61.3, 61.2, 60.4, 59.5, 58.1, 56.8, 49.8, 49.2, 31.0, 26.7, 26.2, 21.0, 19.0, 14.1, 8.7; FTIR (neat film) 3400 (w, br), 2929 (m), 1488 (m), 1460 (m), 1426 (s), 1250 (m), 1213 (s), 1158 (m), 1140 (s), 1105 (s), 1034 (m), 1011 (m), 982 (m), 915 (m), 824 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{43}\text{H}_{47}\text{F}_3\text{N}_3\text{O}_{10}\text{SSiNa}$ (MNa^+) 882.2704, found 882.2694.



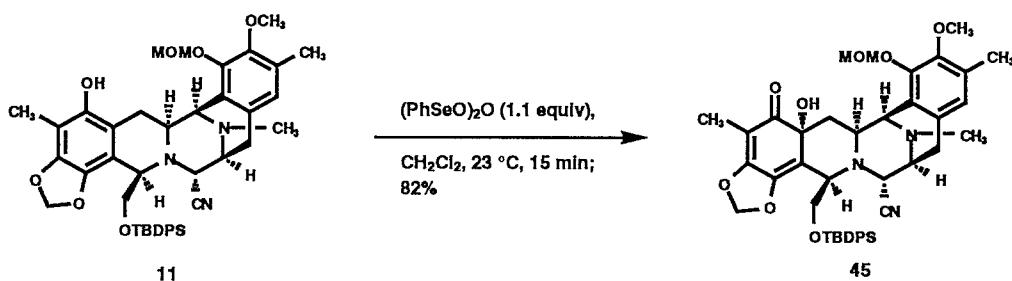
Phenol 44. To a solution of **43** (79 mg, 0.0896 mmol, 1 equiv) and formalin solution (600 μL) in acetonitrile (6 mL) was added solid sodium cyanoborohydride (17 mg, 0.269 mmol, 5.0 equiv), and the solution was stirred at 23 $^\circ\text{C}$ for 30 min. Acetic acid (102 μL , 1.79 mmol, 20 equiv) was added and the reaction was stirred at 23 $^\circ\text{C}$ for a further 1.5 h. The mixture was partitioned between saturated aqueous sodium bicarbonate solution (40 mL) and dichloromethane (30 mL), and the aqueous layer was further extracted with ethyl acetate (2 \times 30 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography (gradient elution: 33% \rightarrow 50% ethyl acetate in hexane) to afford **44** (76 mg, 95%) as a colorless film. R_f 0.60 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +33.5$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.59 (m, 2H, ArH), 7.46–7.22 (m, 8H, ArH), 6.74 (s, 1H, ArH), 5.74 (d, 1H, $J = 1.5$ Hz, OCH_2O), 5.60 (d, 1H, $J = 1.5$ Hz, OCH_2O), 5.35 (d, 1H, $J = 5.7$ Hz, OCH_2O), 5.21 (d, 1H, $J = 5.7$ Hz, OCH_2O), 5.01 (s, 1H, ArOH), 4.89 (m, 1H), 4.60 (d, 1H, $J = 3.0$ Hz), 4.25 (m, 1H), 4.11 (m, 1H), 3.86 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.39–3.30 (m, 3H), 3.09 (dd, 1H, $J = 2.6, 15.2$ Hz, Ar CH_2), 3.01 (dd, 1H, $J = 7.3, 18.2$ Hz, Ar CH_2), 2.74 (d, 1H, $J = 18.2$ Hz, Ar CH_2),

2.30 (s, 3H, NCH₃), 2.05 (s, 3H, ArCH₃), 1.79 (dd, 1H, *J* = 11.3, 15.2 Hz, ArCH₂), 0.97 (s, 9H, *t*-butyl); ¹³C NMR (100 MHz, CDCl₃) δ 150.1, 145.1, 144.4, 141.8, 141.7, 136.7, 135.7, 135.3, 133.0, 132.6, 132.2, 129.7, 127.6, 126.8, 120.3, 118.3, 118.0, 117.1, 116.0, 112.5, 111.9, 106.1, 100.7, 99.9, 77.2, 69.3, 61.6, 61.3, 58.9, 58.2, 56.9, 56.8, 55.0, 48.7, 41.6, 26.7, 25.8, 25.6, 19.0, 14.1, 8.7; FTIR (neat film) 3400 (w, br), 2932 (m), 1466 (m), 1426 (s), 1249 (m), 1213 (s), 1156 (s), 1140 (s), 1107 (s), 1063 (m), 1035 (m), 1013 (s), 992 (s), 976 (s), 958 (m), 934 (m) cm⁻¹; HRMS (FAB⁺) *m/z*: Calcd for C₄₄H₄₉F₃N₃O₁₀SSi (MH⁺) 896.2860, found 896.2872.



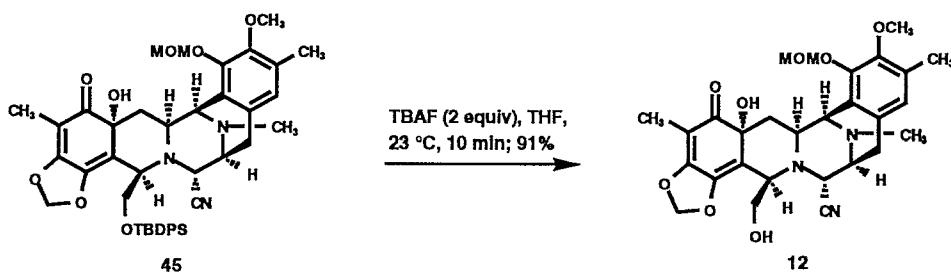
Phenol 11. To a solution of **44** (17 mg, 0.0190 mmol, 1 equiv), lithium chloride (16 mg, 0.380 mmol, 20 equiv), and dichlorobis(triphenylphosphine) palladium (1 mg) in DMF (0.5 mL) was added tetramethyl tin (53 μ L, 0.380 mmol, 20 equiv), and the brown solution was stirred at 80 °C for 2 h. The reaction mixture was partitioned between water (30 mL) and dichloromethane (2 x 20 mL). The aqueous layer was further extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were dried (sodium sulfate) and concentrated. The product was purified by flash column chromatography (gradient elution: 33% → 50% ethyl acetate in hexane) to afford **11** (14 mg, 96) as a colorless film. R_f 0.27 (20% ethyl acetate in benzene); $[\alpha]_D^{23} +11.2$ ($c = 0.55$, CH_2Cl_2); $^1\text{H}\text{NMR}$ (400 MHz, CDCl_3) δ 7.56 (m, 2H, ArH), 7.41–7.25 (m, 8H, ArH), 6.67 (s, 1H, ArH), 5.72 (d, 1H, $J = 1.0$ Hz, OCH_2O), 5.58 (d, 1H, $J = 1.0$ Hz, OCH_2O), 5.51 (s, 1H, ArOH), 5.38 (d, 1H, $J = 5.7$ Hz, OCH_2O), 5.16 (d, 1H, $J = 5.7$ Hz, OCH_2O), 4.57 (d, 1H, $J = 2.9$ Hz), 4.21 (m, 1H), 4.09 (m, 1H), 3.72 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.68 (dd, 1H, $J = 2.1, 10.4$ Hz), 3.38–3.26 (m, 3H), 3.11 (dd, 1H, $J = 2.5, 15.7$ Hz),

ArCH₂), 3.01 (dd, 1H, *J* = 8.9, 17.9 Hz, ArCH₂), 2.70 (d, 1H, *J* = 17.9 Hz, ArCH₂), 2.31 (s, 3H, NCH₃), 2.25 (s, 3H, ArCH₃), 2.06 (s, 3H, ArCH₃), 1.89 (dd, 1H, *J* = 12.1, 15.7 Hz, ArCH₂), 0.90 (s, 9H, *t*-butyl), +3.1% nOe of ArH upon irradiation of ArCH₃; ¹³C NMR (100 MHz, CDCl₃) δ 149.0, 147.4, 145.3, 144.3, 136.3, 135.7, 135.4, 133.2, 130.9, 130.5, 129.6, 129.5, 127.5, 125.0, 118.6, 112.5, 112.1, 105.7, 100.5, 99.8, 68.5, 61.5, 59.7, 58.8, 57.7, 56.9, 56.5, 55.4, 41.7, 26.6, 26.2, 25.5, 18.9, 15.8, 14.2, 8.7; FTIR (neat film) 3400 (w, br), 2928 (s), 2855 (s), 1459 (s), 1432 (s), 1156 (m), 1106 (s), 1061 (m), 1046 (m), 1023 (m), 967 (m), 926 (m) cm⁻¹; HRMS (FAB⁺) *m/z*: Calcd for C₄₄H₅₁N₃O₇SiNa (MNa⁺) 784.3394, found 784.3367.



Hydroxy Dienone 45. To a solution of **11** (40 mg, 0.0525 mmol, 1 equiv) in dichloromethane (6 mL) was added benzeneseleninic anhydride (21 mg, 0.0578 mmol, 1.1 equiv), and the purple solution was stirred at 23 °C for 15 min. The mixture was quenched with saturated aqueous sodium bicarbonate solution (6 mL) before it was partitioned between saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (2 x 20 mL). The aqueous layer was further extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 33% → 50% ethyl acetate in hexane) to afford **45** (33 mg, 82%) as a colorless film. *R*_f 0.27 (50% ethyl acetate in hexane); $[\alpha]_D^{23} +148.2$ (*c* = 0.50, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.7–7.3 (m, 10H, ArH), 6.54 (s, 1H, ArH), 5.28 (s, 1H, OCH₂O), 5.23 (s, 1H, OCH₂O), 5.02 (d, 1H, *J* = 5.7 Hz, OCH₂O), 4.99 (d, 1H, *J* = 5.7 Hz, OCH₂O), 4.46 (d, 1H, *J* = 2.8 Hz), 4.35 (dd, 1H, *J* = 2.8, 14.5 Hz), 4.05–3.95 (m, 2H), 3.88 (m, 1H), 3.79 (m, 1H), 3.63

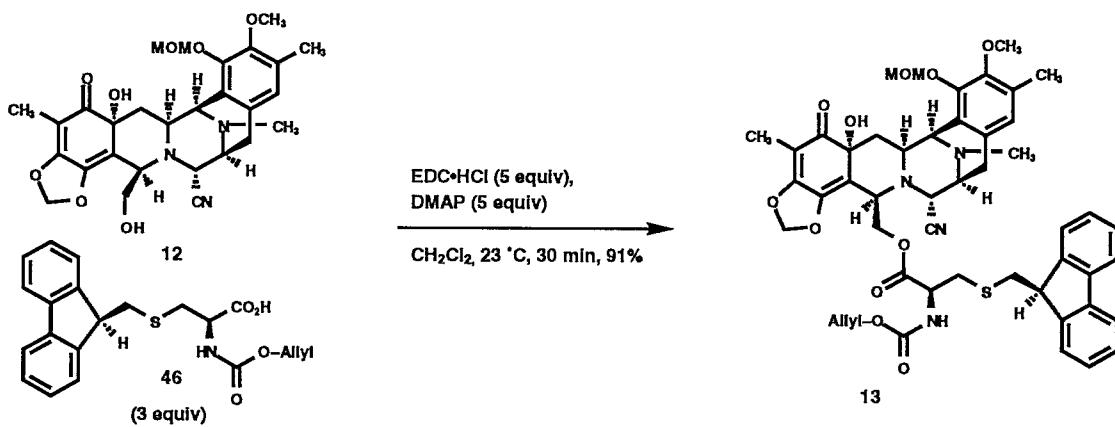
(s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 2.90 (dd, 1H, *J* = 8.7, 17.8 Hz, ArCH₂), 2.39 (d, 1H, *J* = 17.8 Hz, ArCH₂), 2.23 (s, 3H, NCH₃), 2.21 (m, 1H, CH₂COH), 2.19 (s, 3H, ArCH₃), 2.03 (m, 1H, CH₂COH), 1.73 (s, 3H, CH₃), 1.10 (s, 9H, *t*-butyl); ¹³C NMR (100 MHz, CDCl₃) δ 200.9, 160.2, 148.6, 148.0, 137.7, 135.8, 135.6, 133.6, 132.9, 130.5, 130.2, 129.8, 129.7, 129.6, 129.5, 127.7, 127.6, 127.5, 125.1, 124.4, 117.2, 113.5, 100.2, 99.1, 77.2, 72.9, 64.3, 60.3, 59.7, 59.6, 58.9, 57.7, 56.8, 56.5, 56.2, 55.3, 55.2, 42.6, 41.6, 41.3, 35.6, 26.9, 25.8, 25.6, 21.0, 19.4, 19.0, 15.8, 14.2, 7.0; FTIR (neat film) 3500 (w, br), 2929 (s), 1634 (s), 1428 (m), 1377 (m), 1346 (s), 1330 (s), 1232 (m), 1145 (s), 112 (s), 1065 (s), 1054 (s), 1034 (s), 1014 (s), 998 (m), 925 (s), 823 (m) cm⁻¹; HRMS (FAB⁺) *m/z*: Calcd for C₄₄H₅₁N₃O₈SiNa (MNa⁺) 800.3340, found 800.3313.



Diol 12. To a solution of **45** (30 mg, 0.0386 mmol, 1 equiv) in THF (4 mL) was added tetrabutylammonium fluoride (1 *M* solution in tetrahydrofuran, 77 μ L, 0.0772 mmol, 2.0 equiv), and the solution was stirred at 23 °C for 10 min. The mixture was partitioned between saturated aqueous sodium chloride solution (30 mL) and ethyl acetate (3 x 20 mL). The aqueous layer was further extracted with dichloromethane (2 x 20 mL), and combined organic layers were dried (sodium sulfate) and concentrated. The residue was purified by flash column chromatography (gradient elution: 75% \rightarrow 100% ethyl acetate in hexane) to afford **12** (19 mg, 91%) as a colorless film. *R*_f 0.25 (75% ethyl acetate in hexane); $[\alpha]_D^{23} +156.2$ (*c* = 0.11, CH₂Cl₂); ¹HNMR (500 MHz, CDCl₃) δ 6.72 (s, 1H, ArH), 5.86 (s, 2H, OCH₂O), 5.12 (s, 2H, OCH₂O), 4.10 (m, 2H), 3.92 (s, 3H, OCH₃), 3.88 (m, 1H), 3.80 (m, 1H), 3.62 (m, 1H), 3.52 (s, 3H, OCH₃), 3.34 (m, 1H),

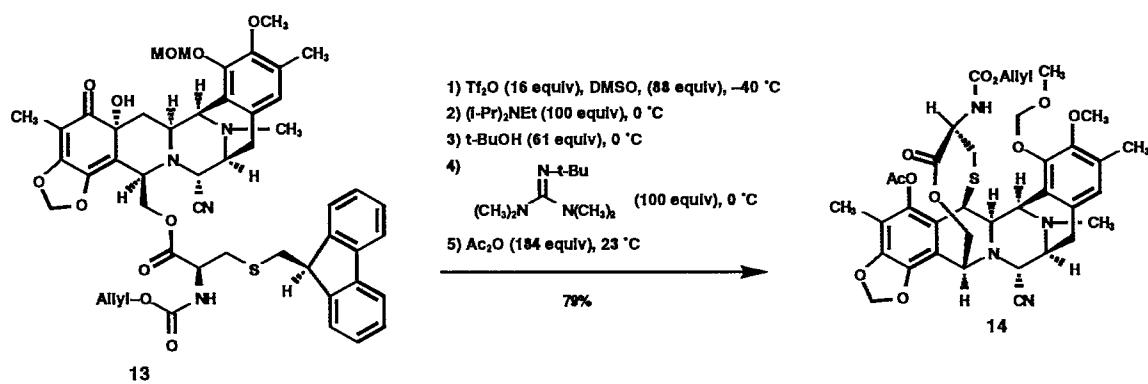
3.04 (dd, 1H, J = 7.7, 18.0 Hz, ArCH₂), 2.68 (m, 1H), 2.62 (d, 1H, J = 18.0 Hz, ArCH₂), 2.32 (s, 3H, NCH₃), 2.24 (s, 3H, ArCH₃), 2.21 (m, 1H, CH₂COH), 2.00 (dd, 1H, J = 8.5, 15.1 Hz, CH₂COH), 1.80 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 198.7, 158.9, 148.8, 148.4, 140.4, 131.3, 130.3, 125.4, 123.0, 116.9, 111.1, 104.3, 101.6, 99.4, 77.2, 70.3, 61.7, 60.5, 58.5, 58.0, 57.6, 57.2, 55.2, 41.6, 36.3, 25.6, 15.7, 7.2; FTIR (neat film) 3450 (w, br), 2926 (s), 1645 (s), 1417 (m), 1378 (m), 1345 (s), 1234 (m), 1157 (m), 1133 (m), 1089 (m), 1059 (m), 1038 (m), 995 (m), 970 (m), 954 (m), 924 (m) cm⁻¹; HRMS (FAB⁺) *m/z*: Calcd for C₂₈H₃₃N₃O₈Na (MNa⁺) 562.2165, found 562.2173.

Final Steps



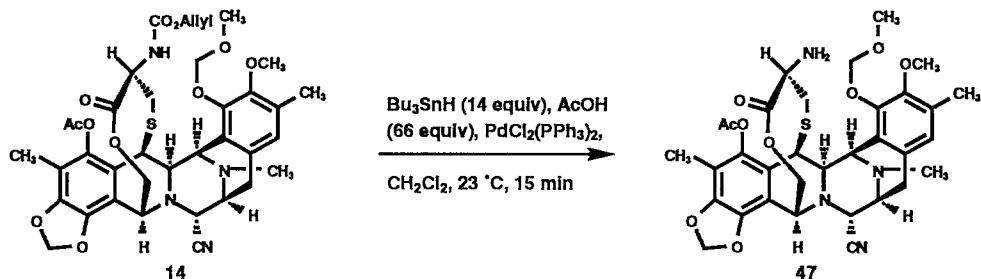
Ester 13. To a solution of alcohol **12** (9.0 mg, 0.0167 mmol, 1 equiv) and acid **46** (19 mg, 0.0501 mmol, 3.0 equiv) in dichloromethane (1.5 mL) was added DMAP (10 mg, 0.0835 mmol, 5.0 equiv) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide•HCl (16 mg, 0.0835 mmol, 5.0 equiv), and the resulting solution was stirred at 23 °C for 1.5 h. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (2 x 20 mL), and the aqueous layer was further extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by flash column chromatography

(gradient elution: 50 → 60% ethyl acetate in hexanes) to afford **13** (13.7 mg, 91%). R_f 0.15 (50% ethyl acetate in hexanes); $[\alpha]_D^{23} +200$ ($c = 0.2$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 7.75 (m, 2H, ArH), 7.62 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.30 (m, 2H, ArH), 6.63 (s, 1H, ArH), 5.90 (m, 1H, vinyl H), 5.74 (s, 1H, OCH_2O), 5.71 (s, 1H, OCH_2O), 5.52 (d, 1H, $J = 8.3$ Hz, NH), 5.32 (d, 1H, $J = 16.7$ Hz, vinyl H), 5.22 (d, 1H, $J = 10.0$ Hz, vinyl H), 5.10 (m, 2H, OCH_2O), 4.57 (m, 2H), 4.50 (m, 1H), 4.23 (dd, 1H, $J = 6.2, 11.2$ Hz), 4.04 (m, 1H), 4.00 (dd, 1H, $J = 2.5, 13.3$ Hz), 3.93 (m, 1H), 3.84 (m, 3H, OCH_3), 3.49 (m, 3H, OCH_3), 3.24 (m, 1H), 3.08 (m, 3H), 2.95 (m, 3H), 2.44 (d, 1H, $J = 18.1$ Hz), 2.36 (dd, 1H, $J = 5.8, 15.0$ Hz), 2.25 (s, 3H, NCH_3), 2.20 (s, 3H, ArCH_3), 1.83 (dd, 1H, $J = 9.4, 15.0$ Hz, C(OH)-CH), 1.78 (s, 3H, CH_3), ^{13}C NMR (100 MHz, CD_2Cl_2) δ 198.7, 170.6, 158.4, 155.8, 149.0, 148.9, 146.1, 142.8, 141.4, 133.0, 131.5, 130.5, 128.0, 127.4, 125.5, 125.1, 123.4, 120.2, 118.0, 117.6, 108.5, 104.6, 102.1, 99.7, 70.9, 66.7, 66.3, 61.2, 60.4, 57.9, 57.2, 56.5, 56.0, 55.7, 54.2, 47.3, 41.5, 37.3, 35.6, 25.9, 15.9, 7.5; FTIR (neat film) 3400 (w, br), 2921 (m), 1722 (s), 1650 (s), 1448 (m), 1378 (m), 1346 (s), 1251 (m, 1234 (m), 1208 (m), 1205 (m), 1157 (m), 1133 (m), 1054 (m), 1040 (m), 1033 (m), 995 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{49}\text{H}_{52}\text{N}_4\text{O}_{11}\text{SNa}$ (MNa^+) 927.3251, found 927.3255.

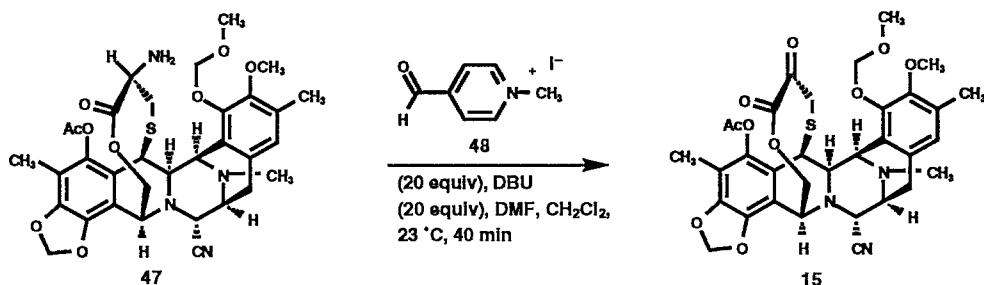


Lactone 14. To a solution of triflic anhydride (8 μL , 0.0476 mmol, 16.5 equiv) in dichloromethane (2.6 mL) at -78 °C was added DMSO (18 μL , 0.254 mmol, 88 equiv), and the solution was stirred at -78 °C for 15 min. A solution of **13** (2.6 mg, 0.00287

mmol, 1 equiv) in dichloromethane (2.6 mL) was added dropwise to the reaction mixture, which was then stirred at -40 °C for 45 min. To the yellow/green reaction mixture was added diisopropylethylamine (51 μ L, 0.288 mmol, 100 equiv), and the yellow solution was stirred at 0 °C for 45 min before excess Swern reagent was quenched by the addition of *t*-butyl alcohol (13 mg, 0.176 mmol, 61 equiv) at 0 °C. *t*-Butyl-tetramethyl guanidine (49 μ L, 0.288 mmol, 100 equiv) was added to the solution which was stirred at 23 °C for 1.5 h, during which time the solution turned near-colorless. Acetic anhydride (50 μ L, 0.530 mmol, 184 equiv) was added, and after 1 h at 23 °C, the reaction mixture was filtered through a short column of silica gel, eluting with 50% ethyl acetate in hexanes. The filtrate was concentrated, and the residue was purified by flash column chromatography (gradient elution: 25 → 33% ethyl acetate in hexanes) to give **14** (1.7 mg, 79%). R_f 0.40 (50% ethyl acetate in hexanes); $[\alpha]_D^{23} -6.0$, ($c = 0.083$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.80 (s, 1H, ArH), 6.09 (d, 1H, $J = 1.4$ Hz, OCH_2O), 6.00 (d, 1H, $J = 1.4$ Hz, OCH_2O), 5.93 (m, 1H, vinyl H), 5.32 (dd, 1H, $J = 1.4, 17.0$ Hz, vinyl H), 5.23 (d, 1H, $J = 9.9$ Hz, vinyl H), 5.22 (d, 1H, $J = 5.2$ Hz, OCH_2O), 5.14 (d, 1H, $J = 5.2$ Hz, OCH_2O), 5.03 (d, 1H, $J = 13.2$ Hz), 4.83 (d, 1H, $J = 9.3$ Hz), 4.52 (m, 3H), 4.31 (m, 2H), 4.24 (s, 1H), 4.16 (m, 2H), 3.74 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.45 (m, 1H, ArCH), 3.40 (m, 1H, ArCH), 2.92 (m, 1H, ArCH), 2.29 (s, 3H, NCH_3), 2.28 (s, 3H, ArCH_3), 2.22 (s, 3H, ArCH_3), 2.13 (m, 1H, ArCH), 2.03 (s, 3H, AcO); ^{13}C NMR (126 MHz, CD_2Cl_2) δ 170.7, 168.9, 166.9, 155.6, 150.2, 148.8, 146.1, 141.5, 140.8, 133.5, 132.2, 130.7, 125.3, 120.8, 118.3, 117.9, 113.9, 102.6, 99.5, 66.1, 61.7, 61.0, 60.6, 60.0, 59.6, 59.4, 57.8, 55.4, 55.0, 54.2, 42.1, 41.4, 33.2, 30.1, 24.1, 20.6, 16.0, 14.4, 9.7; FTIR (neat film) 3450 (w, br), 2930 (m), 1760 (s), 1724 (s), 1515 (m), 1507 (m), 1488 (m), 1456 (m), 1436 (m), 1194 (s), 1089 (m), 1062 (m), 1053 (m), 997 (m), 915 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{37}\text{H}_{42}\text{N}_4\text{O}_{11}\text{SNa}$ (MNa^+) 773.2469, found 773.2466.



Amine 47. To a solution of **14** (5.0 mg, 0.00666 mmol, 1 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.5 mg), and acetic acid (4 μL , 0.0666 mmol, 10 equiv) in dichloromethane (1 mL) was added tributyltin hydride (9 μL , 0.0333 mmol, 5.0 equiv), and the brown solution was stirred at 23 $^\circ\text{C}$ for 5 min. The reaction mixture was directly loaded onto a silica gel column, and the product was purified by flash column chromatography (gradient elution: ethyl acetate \rightarrow 4% isopropyl alcohol in ethyl acetate) to give amine **47** (3.6 mg, 84%). R_f 0.25 (ethyl acetate); $[\alpha]_D^{23} +10$ ($c = 0.10$, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 6.73 (s, 1H, ArH), 6.08 (d, 1H, $J = 1.0$ Hz, OCH_2O), 5.99 (d, 1H, $J = 1.0$ Hz, OCH_2O), 5.21 (d, 1H, $J = 3.4$ Hz, OCH_2O), 5.14 (d, 1H, $J = 3.4$ Hz, OCH_2O), 5.02 (d, 1H, $J = 12.0$ Hz), 4.51 (m, 1H), 4.34 (d, 1H, $J = 4.7$ Hz), 4.27 (s, 1H), 4.20 (d, 1H, $J = 3.0$ Hz), 4.13 (d, 1H, $J = 12.0$ Hz), 3.79 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.45 (d, 1H, $J = 4.7$ Hz), 3.41 (m, 1H), 3.31 (m, 1H), 2.92 (m, 2H), 2.29 (s, 3H, NCH_3), 2.25 (s, 3H, Ar CH_3), 2.19 (s, 3H, Ar CH_3), 2.16 (m, 1H), 2.04 (s, 3H, AcO); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 174.7, 149.8, 148.7, 141.4, 140.7, 132.7, 132.4, 132.2, 131.6, 130.8, 128.9, 128.8, 125.4, 125.2, 121.2, 118.4, 114.3, 102.5, 99.5, 61.9, 60.2, 60.1, 59.4, 59.2, 57.7, 55.4, 55.0, 54.6, 42.1, 41.5, 35.1, 30.1, 24.1, 20.6, 19.8, 15.8, 9.7; FTIR (neat film) 3100 (w), 2920 (w), 1760 (m), 1749 (m), 1462 (m), 1454 (m), 1446 (m), 1436 (m), 1423 (m), 1266 (s), 1238 (m), 1197 (m), 1160 (m), 1089 (m) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_9\text{SNa}$ (MNa^+) 689.2257, found 689.2243.



Ketone 15. To a solution of amine **47** (1.0 mg, 0.00150 mmol, 1 equiv) in a mixture of DMF in dichloromethane (1:3 (v/v), 240 μL) was added solid **48** (7.5 mg, 0.0300 mmol, 20 equiv), and the red solution was stirred at 23 °C for 10 min. DBU (4.0 μL , 0.0270 mmol, 18 equiv) was added, and the black suspension was stirred at 23 °C for 7 min before saturated aqueous oxalic acid solution (0.5 mL) was added. The yellow mixture was stirred at 23 °C for 30 min before it was partitioned between saturated aqueous sodium bicarbonate solution (10 mL) and ethyl ether (30 mL). The organic layer was dried (magnesium sulfate) and concentrated, and was filtered through a short plug of silica gel with 50% ethyl acetate in hexanes to give ketone **15** (700 μg , 70%). R_f 0.30 (50% ethyl acetate in hexanes); ^1H NMR (400 MHz, CDCl_3) δ 6.70 (s, 1H, ArH), 6.12 (d, 1H, J = 1.7 Hz, OCH_2O), 6.03 (d, 1H, J = 1.7 Hz, OCH_2O), 5.20 (d, 1H, J = 5.5 Hz, OCH_2O), 5.13 (d, 1H, J = 5.5 Hz, OCH_2O), 5.10 (d, 1H, J = 12.0 Hz), 4.68 (m, 1H), 4.40 (s, 1H), 4.38 (dd, 1H, J = 2.1, 5.1 Hz), 4.22 (dd, 1H, J = 2.1, 10.9 Hz), 4.18 (d, 1H, J = 2.8 Hz), 3.75 (s, 3H, OCH_3), 3.58 (m, 1H), 3.57 (s, 3H, OCH_3), 3.44 (m, 2H), 2.90 (m, 1H), 2.82 (d, 1H, J = 13.3 Hz), 2.71 (d, 1H, J = 17.3 Hz), 2.32 (s, 3H, NCH_3), 2.22 (s, 3H, ArCH_3), 2.17 (m, 1H), 2.16 (s, 3H, ArCH_3), 2.05 (s, 3H, AcO); FTIR (neat film) 2923 (s), 1764 (s), 1730 (s), 1463 (m), 1456 (s), 1447 (m), 1436 (m), 1195 (s), 1160 (m), 1089 (s) cm^{-1} ; HRMS (FAB $^+$) m/z : Calcd for $\text{C}_{33}\text{H}_{36}\text{N}_3\text{O}_{10}\text{S}$ (MH^+) 666.2121, found 666.2124.